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THE BACKGROUND OF OUR NATAL YEAR*

A PRESIDENTIAL ADDRESS

FLOYD E. KEENE, M.D., PHILADELPHIA, PA.

AMONG the jewels which adorn the crown of true happiness, none is more precious than the esteem of one's fellow men. By your mandate, you have bestowed upon me the greatest honor at your command, an honor which I treasure beyond words of expression and one that will sustain me in the years to come. But I cherish even more the gifts which this high office symbolizes, your confidence, your friendship, and from a heart filled with gratitude, I voice my appreciation.

It is my sad duty to record the deaths of one active and three honorary fellows during the past year:

William P. Graves, president in 1931, recognized in this country and abroad as a leader in his specialty, author, wise counsellor, cultured gentleman, and loyal friend whose going leaves a void which cannot be filled.

William L. Richardson, the last of our Founders to answer the final summons, vice-president of the Society in 1885, and honorary fellow since 1903. The esteem in which he was held is evidenced by the honors conferred upon him by his Alma Mater: Professor of Obstetrics and Dean of the Harvard Medical School and Overseer of the College.

George H. Noble, vice-president in 1913, and honorary fellow since 1931, whose professional life covered more than five decades during

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NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

which his attainments were rewarded by high office in civic, state, and national organizations.

William E. Ashton, elected to the Society in 1895 and honorary fellow since 1920, a gifted teacher and an ardent patriot, who attained his ambition to serve as Regimental Surgeon with combat troops, and was the recipient of the Distinguished Service Cross for extraordinary bravery beyond the call of duty.

We pay reverent tribute to these men who, by their works, added luster to our Society and to the profession which they faithfully served.

We celebrate today the fifty-seventh year of our Society's existence, an epoch in our national development characterized, on the one hand, by unprecedented advances in science, invention, and material as well as cultural resources, and on the other, by the accumulation of forces and events so momentous as to threaten our social and economic structure. During this comparatively brief space of time, American medicine has emerged from adolescence to full maturity, with a strength which commands the respect and admiration of the world. The specialties which this Society represents have reached a peak of perfection undreamed of by those pioneers whom we honor as our Founders and to whose inspiration much of our progress is due.

The evolution of this growth, the individual accomplishments of men who were standard bearers in the march of progress and the contributions our Society has made in promoting the welfare of womankind, have been eloquently portrayed on similar occasions, and these masterly records of achievement adorn the pages of our Transactions. For the setting of my theme, I have gone back to the days of 1876, the year which marks the birth of the American Gynecological Society. My purpose is not to dwell upon the accomplishments of the men who were laying the foundations of modern medicine, but rather, by piecing together certain events and conditions of that day, to depict the scene of their activities. Such a theme seems particularly appropriate because of the striking similarity which exists between economic conditions then, our first annual meeting, and now, our fifty-eighth. Furthermore, they were in approximately the same period of the depression cycle of 1873 as we are in that of 1929, and to them the outlook seemed just as dark, the future as uncertain, as it appears to us today.

In his scholarly address on Higher Medical Education, delivered in 1877, William Pepper vividly describes the conditions leading up to the panic of 1873, which, to many writers, was the worst up to that time. "Following the termination of the war in 1865, came a period of inflated prosperity when the development of our country progressed at an incredible rate. The tide of immigration was setting like a mighty flood toward our shores; our railroad system was stretching its iron threads in every direction, weaving its wonderful network at

the rate of 5,000 miles a year; every day witnessed the establishment of new centers of mining and manufacturing industry, or the opening of new fields of agricultural wealth throughout the land; villages and even towns sprang into existence as though at the touch of a magician's wand. In 1873, overproduction and excessive development had reached a point of such extreme tension that it needed but a slight jar to dash to pieces the fictitious prosperity of the country. The crash came and our overgrown industries were prostrated amid the ruins of princely fortunes. Since then scarcely any branch of business has offered sufficient chances of profit to tempt new capital to seek an investment in it." How tragically familiar this sounds to us of the present day!

The crisis came in September of 1873 when the banking house of Jay Cooke and Company announced its failure, and for more than six years we lived in the blight of its aftermath. This failure precipitated a panic in Wall Street. Securities were dumped on the market in huge amounts. Prices tumbled and several brokerage and banking houses closed their doors. There was a mad rush for money among speculators to prevent being sold out by their brokers. A run on the banks started and only by pooling their resources were the national banks of New York able to survive. The Stock Exchange was closed for ten days. The demands of depositors forced the banks to call in their loans. The process of liquidation thus started spread throughout the country. Debtors were unable to meet their obligations. Business after business went into bankruptcy until in a single year more than 5,000 failed. Productive industry was crippled. Factories closed and thousands of workmen were thrown out of employment. Mortgages were foreclosed and farmers lost their homes. Railway traffic dwindled and several roads went into the hands of receivers. Money was hoarded and enormous sums were concentrated in the solvent banks. A period of industrial and financial stagnation set in and lasted for more than half a decade.

The panic of 1873 began in Austria and the United States at about the same time.[1] It followed one of the most remarkable experiences of waste of national resources through war, the sinking of capital in enterprise far beyond the world's immediate needs and changes in the economic order which the world had ever seen. National resources were wasted like water in three wars shortly preceding 1873, the Civil War here, that of Italy against Austria in 1866, and the Franco-Prussian War in 1870.

During the ten years preceding the panic of 1873, the absorption of capital in great enterprise was as great as the waste in war. The railroad industry was the great boom industry both here and abroad. Cheap steel was made possible by the perfection of the Bessemer process and by 1876 the death knell of iron in the heavy metals industries

had been rung. Steel manufacture developed at a rapid rate. The oil fields of Pennsylvania had been prospected and developed after the Civil War and by 1876, kerosene became the leading household illuminant in America.

From 1876 to 1878 there were a number of inventions which laid the foundation for much of the national wealth created since that time. Alexander Graham Bell invented the telephone in 1876. At the Centennial Exposition, held the same year in Philadelphia to commemorate the one hundredth anniversary of our independence, a few experimental arc lights were exhibited, and we had the crude beginning of our giant electric light and power industry which in turn revolutionized all industry. The talking machine was invented by Edison in 1878, the typewriter in the same year, and a few months before, Otto of Germany perfected a gas engine which paved the way for the later invention of the automobile. Years were to elapse before the full significance of many of these inventions was to be realized. So revolutionary were some of them that their promoters were ridiculed or bitterly persecuted. Alexander Graham Bell was publicly condemned and his arrest as a fraud and a charlatan was demanded when he sought public support to finance his enterprise.

Our Society was born in a period of the most intense competition. This was the heyday of "laissez faire." Unrivaled natural resources to be tapped, cheap land, cheap labor, boundless opportunity; here were the incentives to build and to do. Production multiplied, prices went down, the struggle for industrial survival was intense. In the exploitation of our natural resources, only the cream was skimmed, and the government policy was one of "hands off." Even the railroads could defy the government, both State and Federal, and argue that they were strictly private enterprises and not subject to regulation.

Following the panic of 1873, students of economics were most unfavorably impressed by the fact that in spite of the great increase in the wealth of the nation there was so much hardship, particularly among the laboring classes and the farmers. Why in the midst of such plenty was there so much misery and discontent? Numerous economic "cure-alls" were advocated and obtained wide support. Among them were Populism, Marxian Socialism and Henry George's Single Tax. Populism was particularly strong in the agricultural West where the farmers ascribed their troubles to the want of sufficient money. "Cheap money" was advocated. Inflation and higher prices through the extensive issue of legal tender paper money and free coinage of silver were demanded. The Populist platform included demands for government ownership of railroads, an income tax, and postal savings banks.

As a result of this agitation, the United States went off the single gold standard in 1876 and adopted bi-metallism. Our country had been on a gold standard from 1873 when free coinage of silver dollars on a 16 to 1 basis had been stopped. The silver mining interests supported agitation backed by other currency inflation groups and finally over the veto of President Hayes, the act was passed requiring the United States government to purchase a fixed amount of silver bullion each month and coin it into dollars. Fortunately our government maintained a stable currency by promising to redeem the silver dollars in gold and the number of dollars coined was restricted.

The year 1876 was marked by two other events which stirred the public to a high pitch of excitement. The first of these was the Battle of the Little Big Horn on June 25 when General Custer and his 262 men were massacred by Sitting Bull and his Sioux Indians. The second event was the presidential election.

It has been said, and our history supports the contention, that no political party which is in power during a severe economic depression can be reelected if the election occurs while times are still hard. Such would have been the case in 1876 but for the most extraordinary circumstances, and opinions still differ with respect to the outcome. General Grant had been elected president in 1868 and reelected in 1872. The panic of 1873 added to the bitterness and hardship of the reconstruction period in the southern states. The Republicans nominated Rutherford B. Hayes and their platform was replete with platitudes regarding liberty, equality, civil and political rights. It eulogized the deeds of the party and affirmed that the protection of all citizens was a sacred duty. The "Old South" could well boil at such statements, suffering as they were from economic prostration and "carpet bagger" controlled elections.

Samuel J. Tilden was the Democratic nominee. Their platform was the most elaborate declaration of principles ever put forth by a national convention. Much of it was cast in the form of an indictment against the Republican Party which had been in control for sixteen years, and was in vituperative language. "The paramount and all pervading sentiment," as one historian puts it, "was the necessity for reform in the administration of the government."[2]

It is interesting to note that two minor parties also selected candidates for the presidency. The first of these was the Greenback Party which advocated the payment of government obligations in greenbacks and an increase in the volume of currency by the issue of paper money. The other was the Prohibition Party which demanded the prohibition of traffic in intoxicating liquors. Neither party was strong enough to choose a single elector.

The elections of 1874 had gone strongly against the Republicans and since the Democrats had put up strong candidates, and because of the

general disgust at corruption in the government service, they stood an excellent chance of winning at the polls. On the morning after election, the newspapers announced a Democratic victory. Most of the Republicans conceded it. Tilden had 184 electoral votes, one less than the number required. Hayes had 166 votes and needed those of three southern Democratic states, Florida, South Carolina, and Louisiana, to give him the required number for election. These he finally got by methods which were anything but savory.

The election aroused a storm of protest, and intense excitement prevailed throughout the country. There were threats of violence to prevent the installation of Mr. Hayes. It was not until two days before inauguration that Hayes and Wheeler were notified by a special commission that they had been duly elected. Never had a presidential election come so near to precipitating the country into civil war.

In looking back on the year 1876 it is but natural that the greatest emphasis should be placed upon things economic and political, because these matters are uppermost in men's minds when living is difficult and misery abounds. Something should be said, however, of the cultural side of the life of that day. Who were the writers whose works were widely read? Bronson[3] states that the works of six men of letters constitute a large part of the strength and beauty of American literature. Comprising the group are Hawthorne, Longfellow, Emerson, Whittier, Holmes, and Lowell. With the exception of Hawthorne, all were living in 1876, but Longfellow and Emerson had completed their life work. Walt Whitman, whose *Leaves of Grass* appeared in its fifth edition in 1876, had retired to his quiet New Jersey home, broken in health by the strain of his experience as a volunteer army nurse during the Civil War. Edward Eggleston, the earliest American realist, was in his prime. William Dean Howells, editor of the *Atlantic Monthly,* both poet and novelist, was widely read and Henry James was just starting to publish his novel, *Roderick Hudson* appearing in 1875 in the *Atlantic Monthly.* In 1876, Mark Twain was emerging from his western development to national popularity, still later to become one of our great American men of letters. He, perhaps more than any other, typifies in his writing the manners and thought of this period in American history; he was "permeated to the marrow of his bones with the sentiment of democratic society and with loyalty to American institutions."[4] S. Weir Mitchell had already demonstrated his ability as a *litterateur* but, following the advice of Oliver Wendell Holmes that he first establish himself in his profession, he did not fully indulge his literary ambition until after he was fifty years of age, *The Case of George Dedlow* appearing in 1880. James Whitcomb Riley had not settled down to literary production as yet, but was riding around the countryside with a medicine show as one of the principal minstrels.

Our colleges and universities were patronized by only a mere handful of the youth of the nation. The great development of university education was yet to come, but in 1876, Johns Hopkins introduced postgraduate instruction which marked the beginning of the better order of things in our university training.

Medical education in the United States was at a low ebb and stood out in striking contrast with that of other countries. Under no governmental regulation or control, medical schools sprang into existence, some to flourish for a time and die, others to develop into the strong institutions of today. With 65 schools scattered among 24 states, they were located, often, in towns so small as to make clinical instruction impossible, and were manned too frequently by faculties whose business acumen transcended their professional attainments or ability to transmit medical knowledge. The schools existed as private business corporations, dependent upon students' fees for their dividends, and as Pepper states, "were conducted in the interests not of the medical profession, not of the community, certainly not of medical science, but of the members of the faculty alone."[5]

Because of this, competition for patronage was keen and the prospective student was lured by no preliminary appraisal of his fitness to enter the school, by short courses of instruction, by the unwritten but generally understood assurance of success in his final examinations and, in the end, by offering him a document which conferred not only the degree of Doctor of Medicine but also the license to engage in the practice of his profession.

A few schools demanded a preceptorial year, but this was often a mere formality, contributing little or nothing to the students' education. With but three exceptions among the 65 regular schools of Medicine extant at that time, the requirements for a degree consisted of the attendance upon two yearly courses of lectures, each of less than five months' duration. The lectures were purely didactic and no attempt was made to grade them in conformity with the stage of the students' progress in learning. In the larger cities where hospital facilities were available, clinical lectures were given, but attendance was not compulsory and bedside teaching was so rare that "the vast majority of American medical students received the degree in Medicine without even having felt a sick man's pulse or listened to the sounds of the lungs or heart."[5] Dissection was demanded in some of the better schools, but otherwise, practical work was ignored and the microscope as well as the testtube were beyond the reach of the student.

This deplorable state of affairs had been attacked by leaders of the profession and medical organizations but with little effect, since those in authority were haunted by the fear of empty halls should a change

be made. Standing alone for several years in the attempt to advance medical education was the Chicago Medical College, later to become affiliated with Northwestern University, organized in 1859 "for the express purpose of testing the practicability of establishing a school with a thoroughly graded and consecutive system of instruction,"[6] and a curriculum embodying progressive thought in medical education. A similar course of action was adopted by Harvard in 1871 and Syracuse four years later. In 1877, other medical schools joined the ranks of progress, among which, I am proud to say, was the University of Pennsylvania.

In matters pertaining to Public Health and Preventive Medicine, the United States lagged far behind such countries as France, Germany, Belgium, and particularly England whose efforts in this direction were receiving world acclaim. Through its army and navy activities and publications, the United States government had made large contributions to sanitary science, but, as shown by the survey of Bowditch,[7] three-fourths of the States exhibited a woeful lack of interest in the health of their citizens, and among these were New York and Pennsylvania. In 1876, only twelve states had established Boards of Health and most of these were not functioning as they should because of inadequate appropriations. Methods directed toward the prevention of contagious diseases were entirely lacking in many states, and "nearly two-thirds of the people of the Union were living in a senseless disregard" of the purity of the water they were drinking.

The outstanding event in Medicine during 1876 was the International Medical Congress, held in Philadelphia under the Presidency of Samuel D. Gross, to celebrate the progress of American medicine during the century of our national life. Among the foreign representatives was Joseph Lister, who only a few years before had enunciated a doctrine which was destined to revolutionize surgery and to bring him undying fame. He came, not as a conqueror, but as a missionary to nurture the seed of truth in a soil of scorn and doubt. In his address as Chairman of the Surgical Section, he stated, with the simplicity of the truly great, that he would "be pleased, indeed, if the discussion which is about to take place should have the effect of strengthening the belief of the profession in the truth, the value and the practical application of the principles of antiseptic surgery," principles which, in the good they have wrought, vie with those of Christianity itself.

Amid such surroundings our Society was born, our Founders lived and worked. Measured in terms of time, these events are but those of yesterday, events within the memory of some of our Fellows and the life-span of nearly one-half; gauged by the measure of achievement,

they seem to belong to the distant past. Again our country is in the valley of despair but if we climb to the hilltop and view the events from then to now, we are awed by the splendor of a nation's strength which inspires our hope and faith.

We glory in the fame of Sims, of Emmett, of Atlee who opened the portals of American Gynecology, we marvel at the accomplishments of the men of that day with such meager resources at their command, but we cherish the spirit which animated their lives, courage, sincerity, self-sacrifice, devotion to duty, and this is the heritage they have handed down to us.

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ANATOMICAL VARIATIONS IN THE FEMALE PELVIS AND THEIR EFFECT IN LABOR WITH A SUGGESTED CLASSIFICATION

W. E. Caldwell, M.D., F.A.C.S., and H. C. Moloy, M.D., M.Sc.,
New York, N. Y.

(From the Department of Obstetrics and Gynecology, Columbia University, and the Sloane Hospital for Women)

INTRODUCTION

THIS study is limited to the anatomical variations in the pelvic architecture which are thought to be caused by racial, sexual, or other complex inherited influences rather than by pathologic changes in the bones themselves. We wish to show that these variations may be segregated into groups displaying common architectural features which permit a classification of pelves on the basis of morphology. From observations on the dry pelvis and roentgenologic examinations of the living subject, the relation of these variations to pelvic capacity, their obstetric significance, their clinical recognition, and resulting prognostic importance are discussed.

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NOTE: For lack of space, this paper appears here in abstract form, but the complete article may be found in the Society's Transactions as well as in the author's reprints.

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OBSERVATIONS

Following careful inspection and study of a large series of skeletal remains, we observed that female pelves could be divided into four large groups on the basis of morphology.

The first group represents the so-called normal female pelvis, and for the most part, displays the sexual characters ordinarily attributed to the female sex of man. As early as 1876, Fehling[6] demonstrated the presence of sexual characters in fetal pelves but his observations received scant recognition from the leading obstetric authorities of his time. Thomson[7] in 1899, unacquainted with Fehling's work, again observed these features in the sacrosciatic notch and subpubic angle of fetal pelves and described in considerable detail the sexual differences in the adult male and female pelvis. A clear understanding of these differences is essential in order to identify the changes which occur in pelves displaying an overlap or intermingling of these sexual characters.

This type of variation constitutes our second group, wherein female pelves possess masculine characters, particularly in the posterior aspect of the true pelvis. The masculine type of female pelvis was well known to the earlier obstetricians. Murphy,[8] 1846, ably described the mechanism of labor in this type of female pelvis which "approaches the character of the male pelvis." Yet no accurate account of its anatomical peculiarities exists in obstetric works. Anthropologists have recognized this type for years as a result of the difficulty encountered by field workers in the diagnosis of sex in unknown skeletal material. In 1909, Derry[9] reviewed Thomson's work and drew attention to the occurrence of these male characters in the fore pelvis. Elliott Smith and Wood Jones,[10] during their excavations in Nubia, recognized a number of female pelves which so closely approached the form of the male that the presence of fetal bones within the pelvis alone suggested the true sex of the skeletons. Hart[11] appears to be the first obstetrician to observe this pelvic form which he called the "inverted pelvis" and identified two types, the "ischiopubic," and "iliosacral." The former refers to male characters in the fore pelvis, the latter to the occurrence of these features in the posterior aspect of the true pelvis. He failed to recognize the great frequency of occurrence of these features in living women, and from the limited number of skeletal examples studied, failed to stress the great obstetrical significance of this form of variation. Later Straus,[12] working with Todd's material of known sex, observed that the great prevalence of male characters in female pelves decreased the value of the established criteria of sex as found, for instance, in the size and shape of the sacrosciatic notch. In fact he considered that the diagnosis of sex in unknown skeletal material borders on guesswork, unless the body is examined before maceration occurs. A conception of

the frequency of occurrence of male characters in skeletal material has been suggested by Hrdlička,[13] Hooton,[14] Reynolds,[15] and others.

The third group appears to compare favorably with the transversely contracted or assimilation pelvis carefully described in all modern obstetric texts. Baudelocque[16] was aware of the existence of this abnormality but he considered it a rare form. Dewees,[17] 1826, accurately described the mechanism of labor in a private case possessing this type of pelvis. Although Murphy[8] noted its resemblance to the infantile pelvis and the pelvis of the quadrupeds, Turner[18] in 1886 was the first to draw attention seriously to its "anthropoid" appearance. He believed that it was most frequently observed in the lower races of mankind. We shall later describe in detail the points of resemblance of this interesting pelvic type to the pelvis of the anthropoid apes.

The last group represents the simple flat pelvis of other classifications. This is a rare type and, in contrast to the "anthropoid" type, may be said to possess an ultrahuman form. De Lee[19] considers that rickets is the principle causative factor. Williams,[20] however, has observed this pelvis in robust women with no other evidence of that condition.

In the extremes these four groups possess clearcut anatomical characters which readily distinguish one from the other. But the intermingling of types renders difficult any attempt to gain simplicity in their classification. Throughout this study we have attempted to conform to a uniform method of approach in the analysis of these complex pelvic types. In the following description of a pelvis of neutral sex we define terms and distances which will be repeatedly referred to with reference to the individual forms of variations. It is based essentially on the work of Thomson,[7] Derry,[9, 21] and Straus,[12] and we have correlated their observations in a manner which permits the clinical application of these sound anatomical deductions.

The pelvic girdle is formed by the articulation of the two innominate bones with the sacrum behind and their union in front at the symphysis pubis. Each innominate bone consists of three distinct elements: the ilium, the ischium, and the pubis. Two elements, the pubis and ilium, enter into the formation of the pelvic inlet along the iliopectineal line, assisted by the anterior free margin of the first sacral vertebra posteriorly. Each separate bone potentially possesses inherited peculiarities of form such as sex, race, size or persistence of characters resembling the pelvic form of the anthropoid apes, which may modify the shape of the compact pelvis in whole or in part.

We propose to divide the inlet into an anterior and posterior segment at the widest transverse diameter. The anterior segment may be likened to a triangle on a broad base, the widest transverse diameter. The sides, diverging from the symphysis at an angle of variable size, consist of the superior rami of the pubic bones along the ilio-pectineal

line and the lower (ventral) portion of the ilium. We designate this segment of the inlet "the anterior puboiliac portion" (Fig. 1, B_1).

The posterior segment refers to the obstetric posterior pelvis and is bound in front by the widest transverse diameter, laterally by the midportion of the ilium which forms the summit of the great sacrosciatic notch, and posteriorly by the sacrum. In shape it is flat and rounded laterally by the acute inward curvature of the ilium toward the sacroiliac articulation. We designate the very important midsection of ilium situated between the widest transverse diameter and the sacroiliac articulation on the iliopectineal line, "the posterior iliac portion" of the inlet (Fig. 1, A_1).

Sexual differences as Thomson, Derry, and Straus (loc. cit.) have shown, are pronounced in the posterior iliac portion, although their measurements are not limited to the distance designated by us. Our posterior iliac portion compares favorably with Thomson's "hinder ilium," with Derry's "posterior segment of the pelvic chilotic line," and the posterior aspect of the "lower iliac height" of Straus. We consider that the transverse diameter of the inlet must be the dividing plane in view of its great obstetric significance.

Reference to the diagrammatic representation of this analysis shows that variations in the anterior segment of the inlet may be expected to occur in the length and curvature of the puboiliac portions (Fig. 1, B_1) and in the size of the angle formed by these lateral boundaries at the symphysis (Fig. 1, B_2).

Variations in the posterior segment of the inlet are largely dependent on the length of the posterior iliac portion (Fig. 1, A_1), the size of the sacrosciatic notch (Fig. 1, A_2) and the size, curvature, and inclination of the sacrum (Fig. 1, A_3).

The pelvic outlet is also divided into two segments by the intertuberous diameter. The anterior segment is concerned entirely with the subpubic angle and variations express themselves in the size of the angle between the descending rami of the pubes (Fig. 2, *A*) and also in the length and curvature of the rami and their mode of origin from the inferior aspect of the body of the pubic bone (Fig. 2, *B*). The length of the rami depends on the depth of the true pelvis as measured on the perpendicular from the tuberosity of the ischium along the posterolateral aspect of the obturator foramen to the iliopectineal line (Fig. 2, *C*).

The posterior segment of the outlet represents the obstetric posterior sagittal diameter. Variations which materially affect this diameter occur in the size and shape of the sacrosciatic notch (Fig. 3, *A*) and the inclination of the sacrum. For any fixed inclination of the sacrum, the sacral tip may occupy any position from the extreme forward curvature to the straight variety (Fig. 3, *B, C, D*). A straight sacrum may increase the posterior sagittal diameter beyond average dimensions. The important

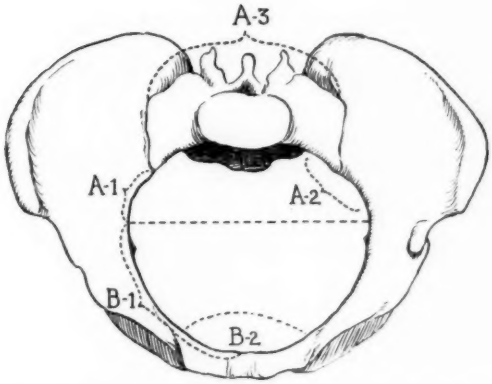


Fig. 1.—A diagrammatic representation of the anatomical variations at the inlet with definition of terms: A_1 The "posterioriliac portion" of the inlet. Variable in length and curvature. A_2 The sacrosciatic notch. Variable in size and shape. A_3 The sacrum. Variable in size, shape, and inclination. B_1 The "anterior pubo iliac" portion of the inlet. Variable in length and curvature. B_2 The angle between the pubo-iliac portions of the fore pelvis. Variable in size.

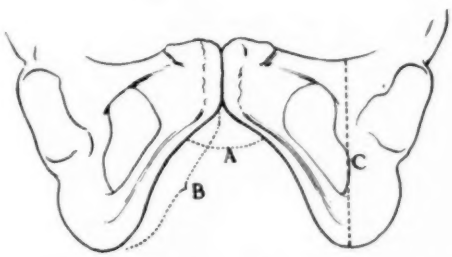


Fig. 2.—A diagrammatic study of the variations which materially affect the fore pelvis. *A*, The subpublic angle. Variable in size. *B*, The length, curvature, and mode of origin of the pubic rami from the body of the pubic bone. *C*, The depth of the true pelvis.

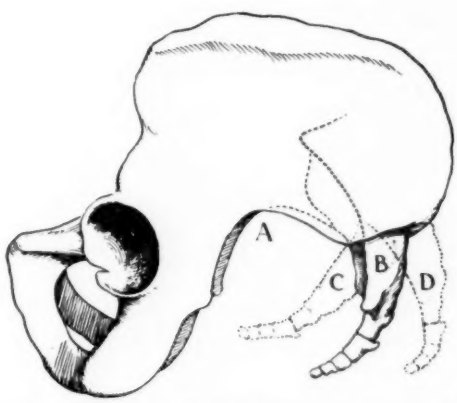
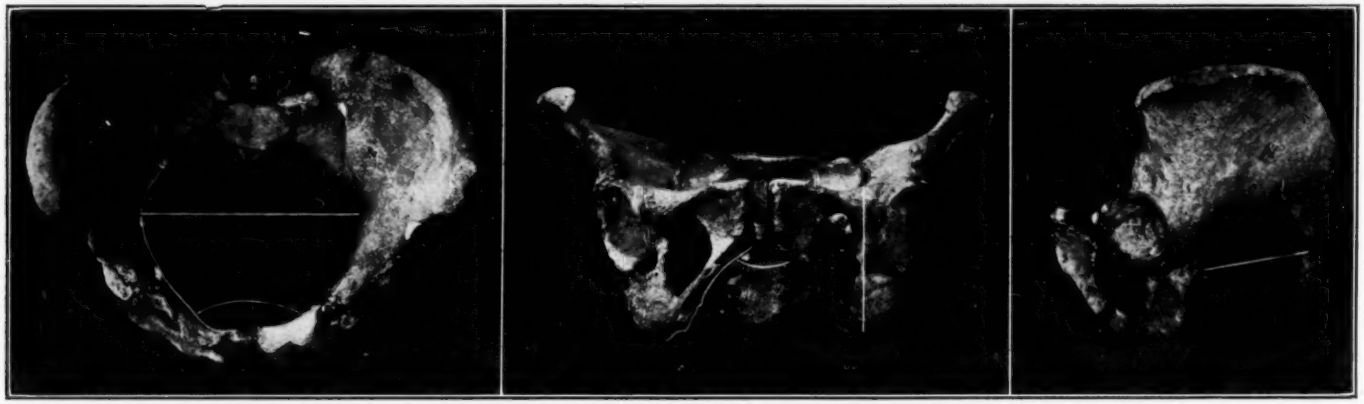


Fig. 3.—A diagrammatic study of the variations which affect posterior pelvic capacity: *A*, The size and shape of the sacrosciatic notch. *B*, Sacrum with normal curvature and inclination. *C*, Acute forward curvature in the terminal segments. *D*, A straight sacrum.

A B C

Fig. 4.—Photographs of the average male pelvis.* In this and succeeding illustrations, the anatomical characters are heavily outlined according to the method shown in Fig. 1. *A*, Inlet view, *B*, anterior view, *C*, lateral view.



A B C

Fig. 5.—Photographs of the average female pelvis.* *A*, Inlet view, *B*, anterior view, *C*, lateral view.

*Courtesy of the American Museum of Natural History.

anatomical factor behind a long or a short posterior sagittal diameter is situated high in the pelvis, in the length of the posterior iliac portion of the inlet, the sacrosciatic notch and the inclination of the sacrum. Occasionally, an acute forward curvature (Fig. 3, *C*) may cause a real labor hindrance but usually in these cases an additional abnormality is found to be present in the subpubic angle or in the posterior aspect of the inlet.

It is to be observed that the length of the anteroposterior diameter of the inlet varies with the length of the puboiliac and iliac portions of the inlet. The transverse diameter depends on the width of the sacrum and the degree of curvature of the inlet at the junction of the puboiliac and iliac segments.

This analysis of the neutral pelvis with definition of terms represents the key followed throughout this study and a clear understanding of the principles discussed will assist in the elucidation of all succeeding types. This method of approach is applied in the following description of the sexual differences in the average male and female pelvis. An understanding of the architectural features of the typical male and female form is essential for the recognition of lesser degrees of variations and other departures from the average form.

The Average Male Pelvis.—Lateral inspection of the compact pelvis reveals a long narrow sacrosciatic notch (Fig. 4, *C*). At the apex of the notch, the lower ilium curves acutely downward to meet a prominent posterior inferior iliac spine and, frequently, a portion of the bone continues to a lower level of articulation with the sacrum before it curves upward to the posterior superior iliac spine. It leaves the impression that a triangular portion of bone has been excised from the apex of the notch. The inclination of the sacrum seems to agree with the general downward slope of the posterior limb of the angle, and hence its position is a forward one in the pelvis. The space between the lower lateral sacral border and the ischial spine is short, usually admitting two fingers, but rarely three. In the living subject this space is bridged by the sacrospinous ligament. This ligament, therefore, is shorter than in the average female pelvis.

The bone tissue between the iliopectineal eminence and the apex of the notch represents the pillar on which the body weight rests and is therefore shorter, broader, and stouter than a corresponding area in the female pelvis (compare Fig. 4, *C* and Fig. 5, *C*). The narrow sacrosciatic notch by medium of this short broad pillar of bone tends to transmit its peculiar form to the inlet and modify it to a like degree in the region of the posterior iliac portion. In the same fashion any characteristic form of the subpubic angle may modify the anterior segment of the inlet.

The narrow subpubic angle presents a characteristic shape in decided contrast to the wide outlet of the female pelvis (compare Figs. 4, *B* and 5, *B*). The descending rami arise from the lower border of the symphysis and pass directly downward at an acute angle to each other. The free

edges are straight, showing no tendency to evert or produce the Norman arch effect so characteristic of the female. The pubic rami are long, and occasionally the intertuberous diameter may be wide. This is made possible by increased depth to the true pelvis as measured on the perpendicular from the tuberosity of the ischium to the iliopectineal line. For males this perpendicular distance equalled 101 mm. as compared to 90 mm. for a similar measurement in the female, as based on averages from 53 white male and 50 white female pelves from Todd's skeletal material at Western Reserve University.

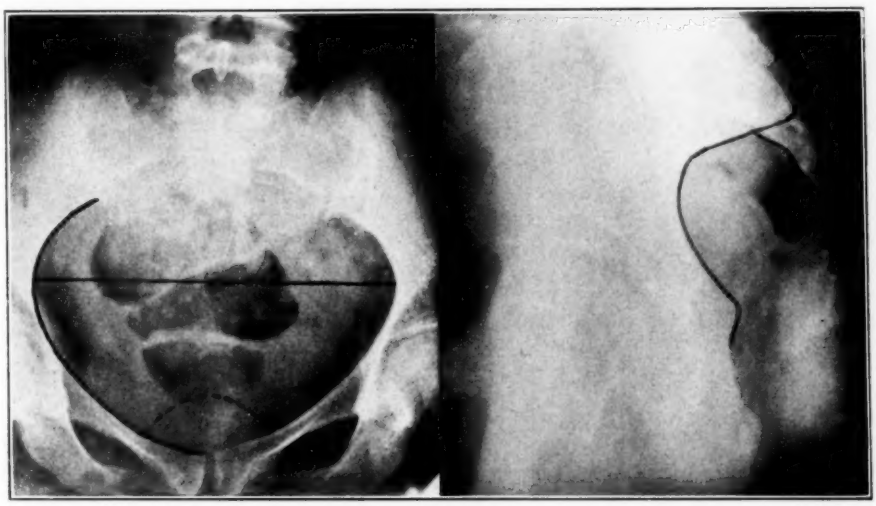
In the average male pelvis, as a result of the factors just mentioned, the symphysis frequently juts forward in advance of the tuberosities of the ischium, producing a boat-shaped effect to the whole anterior pelvis. Thus in association with the forward sacrum there is a converging slope to the four walls of the pelvis, producing a true funneling toward the pelvic outlet.

It is now necessary to study the effect of the narrow subpubic angle and the narrow sacrosciatic notch on the pelvic inlet. Anteriorly, the puboiliac portions of the iliopectineal lines pass backward from the symphysis at a relatively acute angle to each other in a long gentle curve to the widest transverse diameter (Fig. 4, *A*). At this point, the iliopectineal lines curve acutely inward to the sacroiliac articulation, and this distance is short, explaining the anatomical significance of a "short posterior iliac portion." One gathers the impression that the spacious posterior pelvis of the female form could be obtained by cutting through the ilium at the apex of the notch and inserting approximately 2 cm. of flat bone. By this maneuver the iliac portion would be lengthened and the curvature of the iliopectineal line in this region would be less acute and so conform to the shallow, graceful flare of the posterior aspect of the female inlet (Fig. 5, *A*). It is therefore understandable that the widest transverse diameter of the inlet is near the sacral promontory. The latter seems to project forward and encroach on posterior pelvic space to produce the heart-shaped inlet so characteristic of the male.

The Average Female Pelvis.—A lateral view of the pelvis directs attention to the wide sacrosciatic notch (Fig. 5, *C* and Fig. 6, *B*). The lower free portion of the ilium which forms the summit of the notch passes directly backward and downward at almost right angles to the anterior border of the aperture. The posterior limb of the angle of the notch terminates at the posterior superior iliac spine and, as a rule, dips slightly lower opposite the sacral articulation to form the inferior iliac spine. Frequently, the prominence of the inferior iliac spine gives a male character to the shape of the notch but the great length of the iliac portion of the inlet prevents a decrease in the absolute size of the opening. The sacrum tends to follow the posterior limb and the inclination is generally backward in the pelvis. The shallowness and width of the notch necessitate increased bone length in the posterior iliac por-

tion bridging the apex. As a result, the bone tissue between the iliopectineal eminence and the apex of the notch is longer and not so stout or so broad as a corresponding area in the male pelvis (compare Fig. 4, *C* and Fig. 5, *C*). The spacious outlet of the notch signifies increased length of the diameter between the ischial spine and the lower lateral sacral border. This space will usually admit three fingers with ease. The sacrospinous ligaments are long.

The great width of the subpubic angle is in decided contrast to the narrow angle of the male pelvis (Figs. 4, *B* and 5, *B*). The pubic rami arise from the lower lateral border of the symphysis and produce a characteristic Norman arch effect. This peculiarity is increased by a rolling out of the free edges of the rami. The space immediately below the symphysis is broad and the rami are shorter than in the male. This



A *B*

Fig. 6.—Roentgenograms of the average (gynecoid) type of female pelvis in a living woman.* *A*, Inlet view, *B*, lateral view.

latter feature is at least partially explained by the shallowness of the true pelvis. The symphysis does not protrude anteriorly to the degree present in the male pelvis and the whole anterior pelvis is flatter. This brings about the characteristic inclination or slope of the anterior and lateral walls of the true pelvis toward the wide outlet. The walls are either parallel or tend to diverge in contrast to the general convergence of the true pelvis in the male.

The characteristic shape of the pelvic inlet is dependent to a great extent on the various features of the subpubic angle and sacrosciatic notch just described (Figs. 5, *A* and 6, *A*). A view through the inlet

*The image on the single film represents an enlarged shadow of the actual pelvis. This distortion affords difficulty in illustrating types. Stereoroentgenograms are essential and when viewed in a modified stereoscope reconstruct a true optical view of the original pelvis.

shows that the tip of the sacrum and the ischial spines alone are discernible and offer no obstruction to the wide outlet. Above, the puboiliac portion of the inlet flares backward from the symphysis in a broad graceful curve to the widest transverse diameter. Since the posterior iliac portion is long, as a result of the increased bone space over the apex of the sacrosciatic notch, the widest transverse diameter of the inlet has a position that is more anterior to the sacral promontory than in the male. The anteroposterior diameter likewise is more spacious.

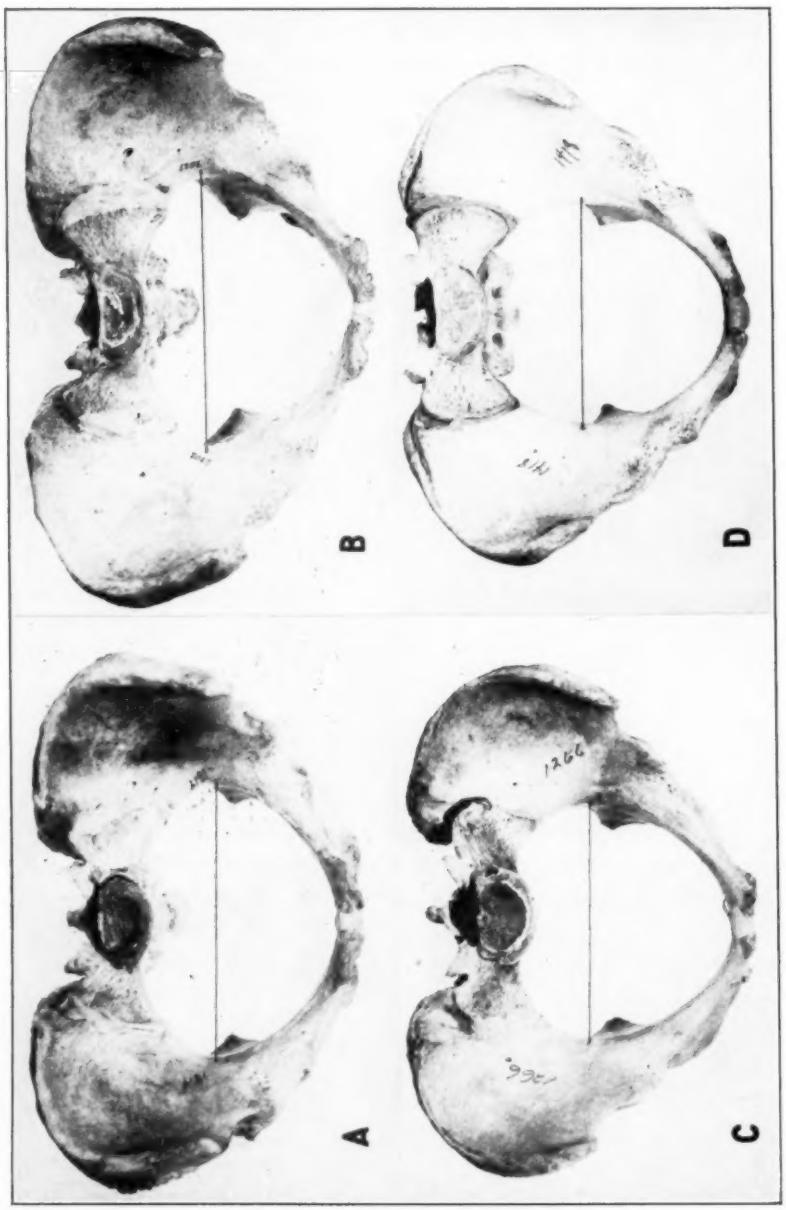


Fig. 7.—Key to the classification with respect to the inlet.* Compare the size of the anterior and posterior segments of the inlet in each group. Also compare the lengths of the puboiliac and iliac portions and size of the angle of the anterior segment as illustrated in Fig. 1. *A*, The platypelloid type, aged sixty; *B*, the android type, aged fifty; *C*, the gynecoid type, aged thirty-three; *D*, the anthropoid type, aged twenty-one.

*Courtesy of Western Reserve University, All Western Reserve material has been restored to the original measurements obtained by Dr. T. Wingate Todd before maceration. We are greatly indebted to Dr. Todd for permission to use these photographs for illustration purposes.

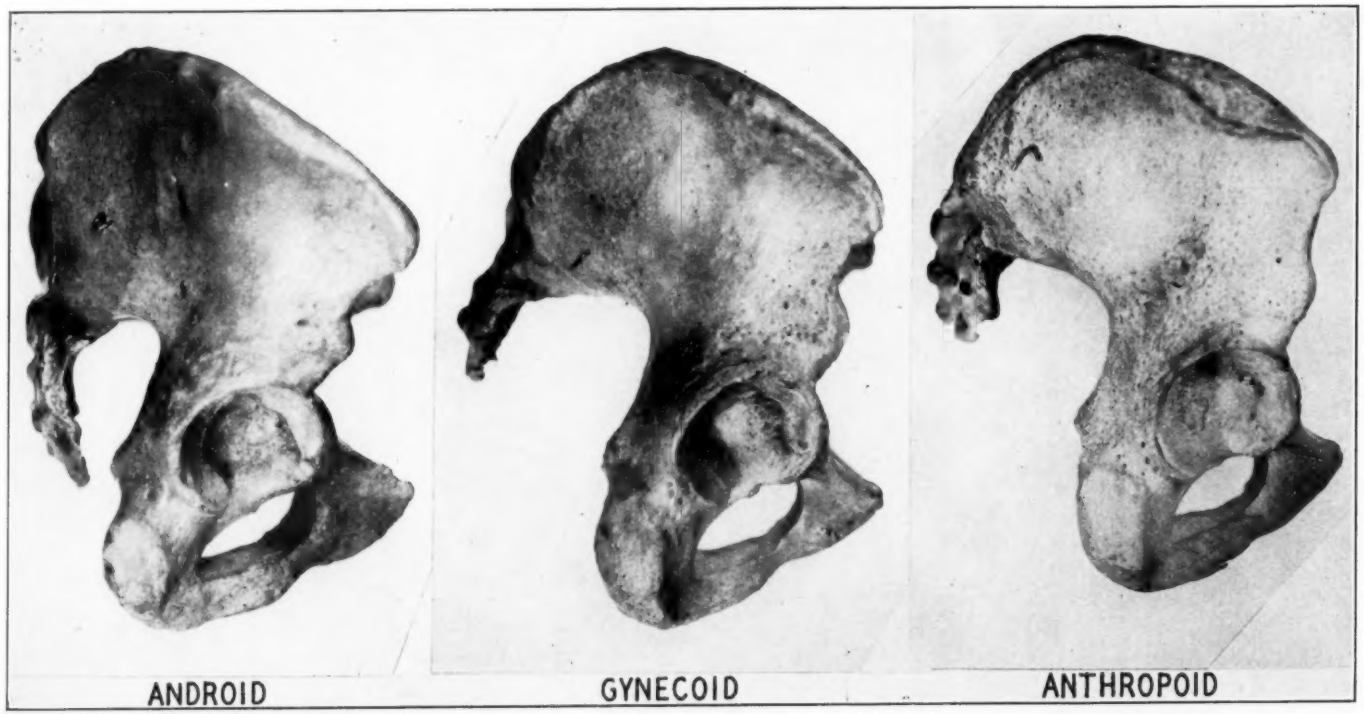


Fig. 8.—Key to the ciassification from the lateral aspects.* *A*, The android type. Note the extreme male type of sacrosciatic notch, aged thirty-five; *B*, the gynecoid type. The sacrosciatic notch is wide. Aged thirty-three; *C*, The anthropoid type. Note the extreme width and shallowness of the sacrosciatic notch, aged twenty-one.

*Courtesy U. S. National Museum.

VARIATIONS IN THE FEMALE PELVIS AND THEIR CLASSIFICATION

We propose to discuss these variations according to the following general classification:

A. The Gynecoid Type (G. gynē-woman).—This is the normal pelvis of other classifications and possesses the well-known anatomical characteristics attributed to the female pelvis. These features have been described under "the average female pelvis." All groups are subdivided on the basis of variations in size of the subpubic angle: (1) With a narrow outlet; (2) with a moderate outlet; (3) with a wide outlet; (4) large or small.

B. The Android Type (G. andēr-man).—These female pelves bear a resemblance to the male sex of man, particularly in the posterior segment of the inlet and the extreme forms simulate the characters described above for the average male pelvis. (1) With a narrow outlet; (2) with a moderate outlet; (3) with a wide outlet; (4) large or small.

C. The Anthropoid Type (G. Anthropos-Man).—These forms bear a resemblance to the pelvis of the anthropoid apes. This resemblance will be discussed in greater detail below. (1) With a narrow outlet; (2) with a moderate outlet; (3) with a wide outlet; (4) large or small.

D. The Platypelloid Type (G. Platy-flat pellis-pelvis).—These pelves are broad and flat, are rare types, and bear no resemblance to the pelvic form of lower mammals. (1) With a narrow outlet; (2) with a moderate outlet; (3) with a wide outlet; (4) large or small.

E. Asymmetrical Pelves.—(1) With a narrow outlet; (2) with a moderate outlet; (3) with a wide outlet; (4) large or small.

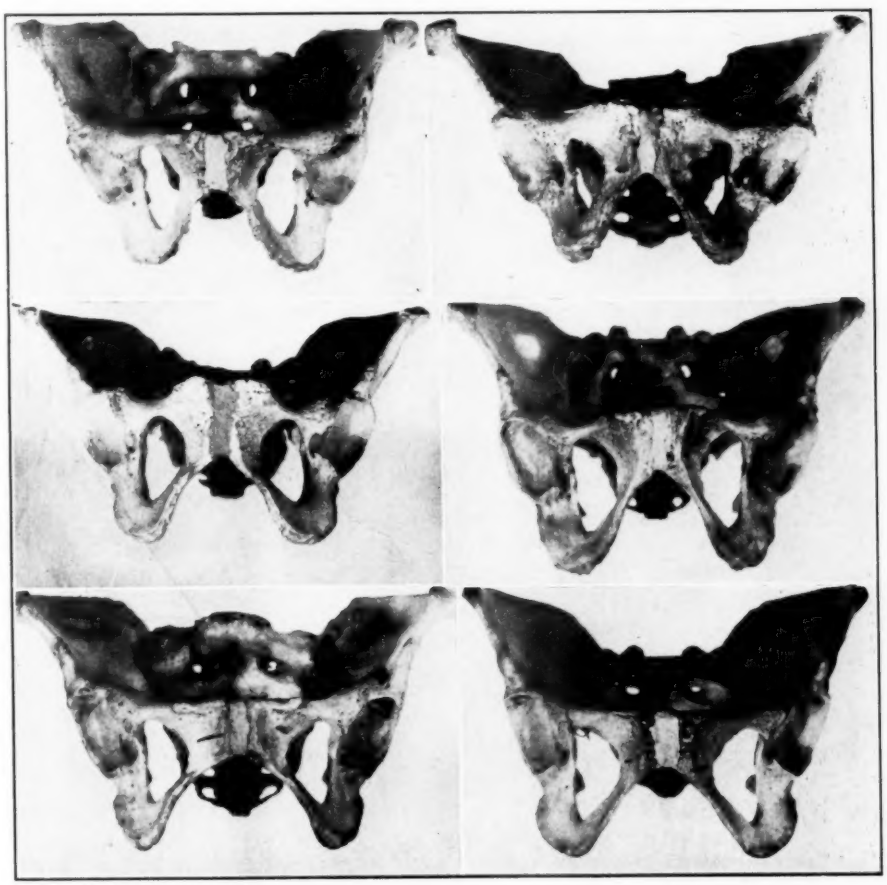
In addition to the asymmetry, the general pelvic shape usually conforms to one of our four types listed above.

In an attempt to correlate the variable factors contrasted in the sexual differences of the average male and female pelvis and diagrammatically illustrated in Figs. 1, 2, and 3, we have based our classification on the shape of the pelvic inlet. This may be visualized to better advantage by reference to Fig. 7. Note the characteristic shape of the inlet as a whole, and particularly the capacity of the posterior segment in the representative example of the four large groups: namely, the "Platypelloid," "Android," "Gynecoid," and "Anthropoid" types. Inspection of Fig. 8 gives an impression of the form of the sacrosciatic notch, the inclination of the sacrum, and an approximate estimate of the posterior iliac portion. It is to be observed that in the four classical types, Figs. 7 and 8, the peculiar form of the posterior segment of the inlet is retained throughout the pelvis and controls the capacity of the posterior aspect of the pelvic outlet.

The fore pelvis remains to be associated with the specific inlet type. Variations in size of the subpubic angle permit a subgrouping into "narrow," "moderate," and "wide" forms, irrespective of the type of inlet. It must be recalled that the pubis may unexpectedly display male, racial, or primitive features, but the inlet may conform to any one

of the four groups mentioned above. The variable factors in the fore pelvis illustrated in Fig. 2 may be recognized in the examples shown in Fig. 9.

The Gynecoid Pelvis.—In this large group are placed all pelves, large, average, or small, whose architectural features are typically female. These characteristics have been discussed under the average female type of pelvis. A visual conception of these features may be gained by reference to Figs. 5 and 6. The term



A *B*

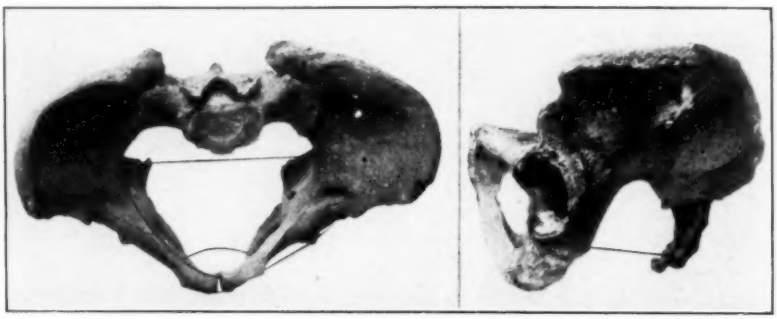
Fig. 9.—Key to the classification in regard to the subpubic angle.* *A*, Narrow, moderate and wide forms showing typical female characters. The pubic rami arise from the lower lateral border of the pubic bone. *B*, Narrow, moderate and wide forms showing rather typical male characters. The rami are straight and arise from the lower border of the pubic bone.

"gynecoid" is therefore applicable. This pelvis is the so-called normal pelvis of other classifications. It is difficult to find a pelvis which is typically female in all portions. A number of slight individual variations in size and shape must be permitted. The sacrosciatic notch may, in the region of the posterior inferior iliac spine, dip downward and produce a male character. On the other hand, as Straus[12] pointed out, a female type of notch may be associated with a short iliac

*Courtesy U. S. National Museum.

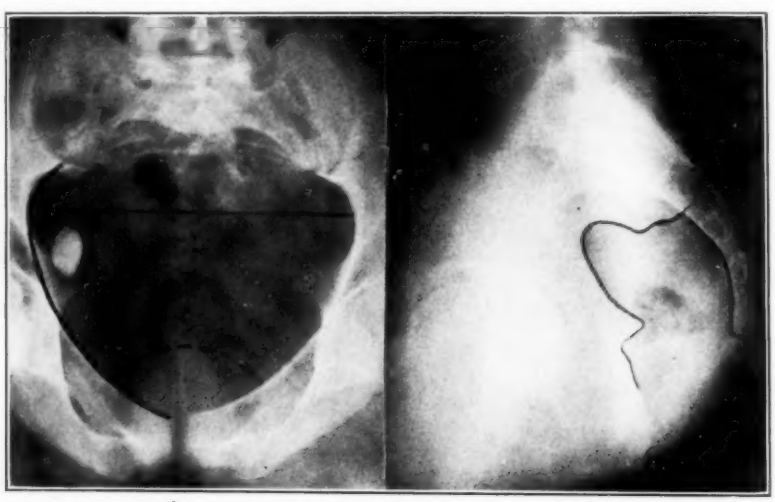
portion. But if the capacity in the two segments of the inlet still conforms to the accepted female type, the presence of these minor android characters does not warrant placing an individual pelvis in another group.

The outlet may display variations from the extreme Norman arch effect to the long straight-bordered subpubic angle of the male. Occasionally the angle is definitely narrowed and yet the pelvis may be female in type in other portions. Such a pelvis is, in reality, a funnel pelvis with a wide posterior sagittal diameter. The latter feature is due to the presence of a broad sacrosciatic notch and long



A *B*

Fig. 10.—Photographs of the android type of female pelvis—sexed by Dr. Hrdlicka.* *A*, Inlet view. Note the similarity in shape to the male inlet, Fig. 4, *A*. B, Lateral view. Note the male type of notch.



A *B*

Fig. 11.—Roentgenograms of the android type of female pelvis in a living woman. *A*, Inlet view. Note the narrow fore pelvis and the decreased capacity of the posterior segment. *B*, Lateral view. Male type of notch.

posterior iliac portion. Occasionally, with a narrow subpubic angle, the puboiliac portions of the anterior segment of the inlet may subtend a narrow angle behind the symphysis, producing a narrow fore pelvis. But if the posterior pelvis is ample, such pelves must be considered gynecoid types with narrow or moderate outlets. Variations in size of the subpubic angle are not dependent on the specific architectural form of the posterior aspect of the inlet.

*Courtesy U. S. National Museum.

The Android Pelvis.—The pelves of this large group are characterized by the presence of one or more well-marked male characters in the inlet. The word "android" is suggested as a suitable group term. Occurring in unknown skeletal material, these forms afford anthropologists great difficulty in determining the sex of the individual. They represent the masculine and funnel types of other classifications and have great obstetric significance. This large group may also be subdivided on the basis of variations in size of the subpubic angle. That this is a logical differential point seems further justifiable when it is realized that the obstetric prognosis improves as the subpubic angle assumes a wide female form. The outlet may compensate for the diminished space in the posterior pelvis.

The lateral view shows the narrow male type of sacrosciatic notch (Figs. 10, *B*, 11, *B*, and 8, *A*). The lower ilium forms the upper posterior boundary of the notch. The distance between the lower lateral border of the sacrum and the ischial spine, which in life is bridged by the sacrospinous ligament, is only of moderate length. The extremely narrow notch illustrated in Fig. 8, *A* clearly indicates why the clinical recognition of a short sacrospinous ligament at once suggests a masculine type of pelvis.

In these extreme forms the sacrum presents interesting features. It is usually wider and straighter than in the gynecoid type. The width is a female character,

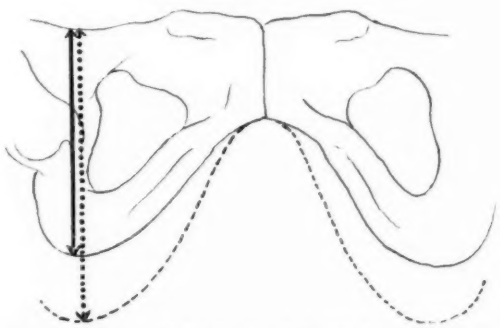


Fig. 12.—A diagram to show that increased depth to the true pelvis usually necessitates long pubic rami. As a result, the intertuberous diameter may reach normal dimensions and hide a dangerous degree of narrowing of the subpubic angle.

the shallowness of the curvatures and straightness are decidedly male. That this erect attitude is a feature common to male sacra can be readily observed from examination of several compact male pelves. Two factors therefore, acting singly or together, determine the position of the sacrum in the posterior pelvis. In the first place, irrespective of the size of the sacrosciatic notch, its peculiar mode of articulation with the ilium may effect an erect (male) forward inclination. Or again, the general inclination may be in agreement with the slope of the posterior iliac limb of the narrow sacrosciatic notch. It matters little which factor is active in the individual pelvis as pelvic capacity is almost invariably decreased.

The narrowing of the subpubic angle may be quite marked but wide forms may occur (Fig. 9). Although the pubic rami are usually straight, a miniature Norman arch effect may be present. The length of the rami depends on the depth of the true pelvis and this is usually increased. The symphysis may protrude considerably in advance of the tuberosities of the ischium. A lateral view of the anterior pelvis may reveal the boat-like effect of the deep pelvis of the male and the superior pubic rami may slope upward toward prominent pubic tuberosities (Fig. 10, *B*). However, occasionally a fore pelvis of this masculine type may be associated with an ample gynecoid posterior inlet segment, in which event the pelvis is typed as gynecoid with a narrow or moderate outlet.

Great variation in depth of the true pelvis occurs. The extreme in averages between male and female represents approximately 10 mm. In the 50 female pelves measured from this standpoint at Western Reserve University, 3 pelves approximately equalled the male average of 101 mm. Seven others ranged between 95 mm. and 98 mm. A proper understanding of the possible effect of increased depth, when there is an associated narrowing of the subpubic angle, is important because of its obstetric significance. This increased depth necessitates increased length to the pubic rami. As a result, the intertuberous diameter may reach normal dimensions and thereby hide a dangerous degree of narrowing of the subpubic angle (Fig. 12). Hence, a fetal head, which might otherwise barely escape through the narrowed outlet of a shallow pelvis, will meet with obstruction at the outlet if the depth of the pelvis is increased, other conditions being equal.

The long straight puboiliac portions of the anterior segment pass backward from the symphysis at an acute angle to each other. This causes a narrow fore pelvis (Fig. 10, *A*). At the widest transverse diameter the short posterior iliac portion of the inlet curves sharply inward to the sacroiliac articulation, placing the widest transverse diameter closer to the sacral promontory than is the case in the average female type. A study of the x-ray films from a similar type in the living subject reveals the same characteristic features (Fig. 11, *A*).

At this point mention may be made of the so-called posterior sagittal diameter as stressed by Williams.[20] In the classical type this diameter is always shortened if the sacrum has a normal curvature. But this does not hold for all cases. The terminal sacrum is subjected to a great variety of curvatures, so that if this diameter is depended upon, misjudgment of the existing abnormality is bound to occur. A straight sacrum may cause this diameter to reach normal dimensions. In other words, the true index of the available posterior space depends upon the conditions existing higher in the pelvis, in the sacrosciatic notch, the inclination of the sacrum, and the length of the posterior iliac portion of the inlet.

The android pelvis with a narrow outlet shows a decrease in pelvic capacity in both the anterior and posterior portions of the inlet. There is also a general convergence of the walls of the true pelvis so that the diminished space present at the inlet increases as the outlet is approached. A wide outlet occurring in this type of pelvis usually infers an ample anterior inlet segment which tends to compensate for the male character in the posterior aspect.

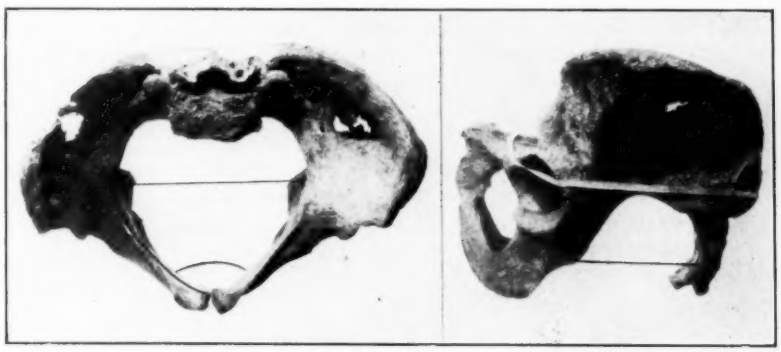
* * * * *

We have noted in living women a number of pelves which in a general way may be said to bear a resemblance to the pelvis of the anthropoid apes. Because of this resemblance the term "anthropoid" is thought to be applicable and descriptive for this special variation. The characteristics of an extreme form may be appreciated from examination of Fig. 13. A comparable type identified from an x-ray examination of the living subject is also shown (Fig. 14).

In this type marked degrees of narrowing of the subpubic angle may occur but, as in any inlet type, the size and shape of the subpubic angle may correspond to any example shown in Fig. 9. The descending rami may be straight, showing an added male form, but the more typical pelves display a miniature Norman arch effect.

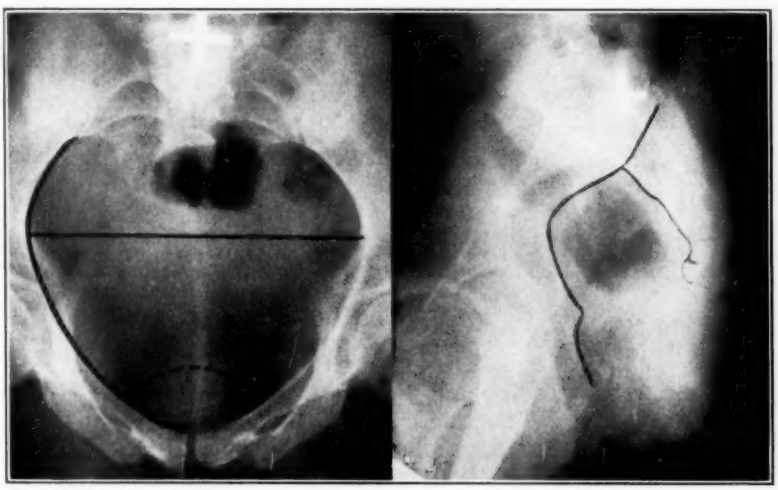
A lateral view of the sacrosciatic notch (Figs. 13, *B* and 14, *B*) reveals an exaggerated female form with increased width and shallowness. The great width is due to an increase in length in that portion of the ilium which forms the summit of the notch in the region of the posterior iliac portion of the inlet. The upper border of the ilium passes backward at right angles to the anterior border of the notch.

On examination of the inlet (Figs. 13, *A* and 14, *A*), the anteroposterior diameter shows an absolute increase and relative or absolute decrease in width of the transverse. The anterior portion of the inlet, if there is an associated narrowing of the subpubic angle, is triangular in shape. The relatively straight iliopectineal lines flare backward from the symphysis acutely and hence limit pelvic capacity in this region. This is in decided contrast to the posterior pelvis. The increased length of the posterior iliac portion causes the terminal segment of the iliopectineal lines to pass backward as a very shallow curve to the sacroiliac articulation and



A *B*

Fig. 13.—Photographs of the anthropoid type of female pelvis.* *A*, Inlet view. The anteroposterior diameter is long; the transverse relatively narrow. *B*, Lateral view. Note the very broad, shallow sacrosciatic notch.



A *B*

Fig. 14.—Roentgenograms of an anthropoid type of pelvis in a living woman. *A*, Inlet view, *B*, lateral view.

places the widest transverse diameter considerably in advance of the sacral promontory. These features combined with the narrowed transverse diameter bear a close resemblance to the characters of the anthropoid pelvis. The long posterior pelvis compensates somewhat for the narrowed anterior portion and the narrow transverse diameter.

The sacrum is long and narrow resembling an African spear-head and frequently displays six segments. It tends to leave the impression that the narrowing, which

*Courtesy U. S. National Museum.

appears to be limited to the alae, is secondary to the general decrease in all transverse diameters throughout the pelvis. It may be recalled that Williams[20] and others believe that assimilation or the occurrence of six sacral segments causes the narrowing present in the subpubic angle. It is doubtful if cause and effect can be so emphatically stated. We have observed marked departures from the narrow type of sacrum and also the number of sacral segments is quite variable. General laws do not affect the individual case.

The promontory of the sacrum is high and the inclination of the plane of the inlet to the horizontal is steeper than in the average pelvis. The sacral surface of the ilium is small in area, quite distally placed toward the posterior aspect of the iliac crest, and the portion of the ilium protruding posteriorly to the articular surface is short. As a rule, the lumbosacral angle is shallower and less marked than in other forms.

The inclination of the sacrum for the most part is backward in the pelvis and the sacrospinous ligaments are long. But, occasionally, the sacrum may slope forward in the pelvis, thereby destroying the compensation effected by the long posterior iliac portion of the inlet. In other cases precisely the same infringement on outlet space is caused by an acute forward curvature in the terminal segments of the

A *B*

Fig. 15.—Photographs to show the effect of variations in the curvature and inclination of the sacrum on posterior pelvic capacity.* *A*, Acute forward curvature, aged forty-four. *B*, The entire sacrum is inclined forward but the curvature is normal, aged twenty-four.

sacrum (Fig. 15). These two variations are not in themselves characteristic of the anthropoid type but may occur unexpectedly in any form. In certain cases, the ischial spines in breadth of base and peculiar shape of the associated portions of the ischium tend to resemble the ischial bulge of the anthropoid apes. In the collection of pelves at Western Reserve University several examples of anthropoid pelves were identified in which the great increase in the length of the anteroposterior diameter appeared to be caused by the long puboiliac portions of the inlet.

Lesser degrees of the anthropoid type produce a round inlet in which the anterior pelvis is female in type. Such pelves blend imperceptibly with the gynecoid forms.

The Platypelloid Pelvis.—This form in other classifications is called the simple flat nonrachitic pelvis (pelvis plana). The broad inlet so characteristic of this type cannot be compared to a similar form in the lower mammals. We believe this special pelvis to be a comparatively rare form of variation as it has been encountered in a very few instances from examination of over 200 complete x-ray studies of

*Courtesy U. S. National Museum.

living women and in Western Reserve material. The great width of the pelvis appears to be its salient characteristic which, in turn, causes the flattened appearance of the inlet. In order to complete a suggested classification and so include this type, we tentatively suggest the term "platypelloid" for this special form.

It is the direct opposite to the anthropoid pelvis, the elliptical shape of the inlet being placed transversely. The transverse diameter is very broad; the anteroposterior diameter relatively short (Figs. 7, *A* and 16, *A*). The puboiliac and iliac portions of the iliopectineal lines are long. It is clearly understood, therefore, that a view of the sacrosciatic notch may optically present a narrowed aperture as a result of foreshortening (Fig. 16, *B*). The first case of this type studied led us to suggest a poor obstetric prognosis. On the basis of the narrow sacrosciatic notch, we thought that we were dealing with a male character in the posterior pelvis. A view of the notches from the posterolateral aspect at once showed that the posterior iliac portion was long and the notch typically female. If this were not true, the transverse diameter could not reach the dimensions it actually attains and it would be necessary to consider it an android type. Several examples from Western Reserve material displayed a very wide sacrum with a decrease in the length

A *B*

Fig. 16.—Roentgenograms of a platypelloid type of pelvis in a living woman. *A*, Inlet view. Note the broad transverse diameter. *B*, Lateral view. The sacrosciatic notch conforms to the female type but appears narrow.

of the terminal iliac portion of the inlet. This anatomic feature did not detract from the flattened appearance. Variations in the subpubic angle, as in all types, may correspond to any example shown in Fig. 9.

The Asymmetrical Types.—The asymmetry is usually caused by a shortening of the posterior iliac portion on one side with an associated narrowing of the corresponding sacrosciatic notch. The puboiliac portion of the affected side may be straighter, resulting in loss of the broad curve of the iliopectineal line in this region and causing slight infringement on anterior pelvic space. The number of observed cases is too small to judge the obstetric significance of this variation. In addition to the asymmetry, the general pelvic type usually conforms to one of our four major groups described above.

DISCUSSION

In 1830, Weber[24] described the first classification of pelves based on morphology alone and identified four groups: oval, round, four-sided, and wedge-shaped. A few years later Stein[25] also divided pelves into

four very similar classes: elliptical in the transverse diameter, round, elliptical in the conjugate diameter, and blunt heart-shaped. In 1886, Turner[18] reviewed these classifications and offered for consideration three large groups: a "Mesatipellic" type in which the transverse diameter was not so greatly in excess of the conjugate, a "Dolichopellic" type in which the conjugate diameter was either longer than the transverse or approached closely to it, and a "Platypellic" type in which the transverse greatly exceeded the conjugate.

It is interesting to compare these three classifications with our four major groups as illustrated in Fig. 7. The wedge-shaped type of Weber and the blunt heart-shaped type of Stein undoubtedly compare favorably with the "android" type of pelvis which, as described elsewhere in this article, represents the occurrence of male characters in the inlet. A comparable group is not present in Turner's classification as he limited his study to the male pelvis in order to avoid the question of the overlap of sexual characters, as the occurrence of female characters in the male sex is not common. Weber and Stein based their observations largely on a study of the female pelvis and naturally describe a form which, in the light of accumulated information since the publication of their results, suggests that they also recognized a type containing male characters.

The four-sided form of Weber and the elliptical type of Stein wherein the conjugate exceeds the transverse agree with Turner's dolichopellic type and in this respect all conform to our "anthropoid" group. Turner[26] keenly observed that his dolichopellic type frequently possessed a long narrow "dolichohieric" sacrum and in this and other respects resembled the pelvis of the anthropoid apes. He considered that it was more frequently observed in the lower races of man and that it presented a "degraded or animalized arrangement" as a result of its anthropoid form.

The ovoid and transversely elliptical types conform to Turner's Platypellic group. Turner, of course, in view of the fact that he was particularly interested in the various races of man, considered that this represented the form that was characteristic of the more civilized and advanced races of mankind. We have utilized his term "Platypelloid" to designate the rare simple flat nonrachitic pelvis of other classifications. This type cannot be compared to any lower mammalian form and in contrast to the anthropoid type may be said to represent an ultrahuman form.

Our gynecoid type compares favorably with the round forms of Weber and Stein and the "Mesatipellic" type of Turner. Criticism may be offered regarding the term "gynecoid." Strictly speaking, it refers to the occurrence of female characters in a male pelvis. We believe the term is justifiable in order to differentiate a female pelvis which conforms to the accepted anatomical standards as far as sexual char-

acters are concerned from the other three large groups. The term "android" has been correctly applied to male characters in the posterior aspect of a female pelvis, thereby accounting for our second large group displaying an overlap of the sexual characters in the female.

In this classification the pelvic inlet becomes the denominator as we have attempted to correlate sound anatomical principles and obstetric significance. Failure to correlate these factors has led to the unavoidable confusion which is evidenced in all present classifications. Criticism of this method may be offered, particularly in the classification of certain forms which possess marked male characters in the fore pelvis. For instance, a gynecoid, android, anthropoid or platypelloid type with a narrow outlet may display clinically a narrow subpubic angle, wide symphysis, steep pubic inclination and a narrow anterior inlet segment. These forms in other classifications may be termed "funnel" or "male" types. Note that the terms "funnel" or "male" fail to describe the type of inlet which may be present, and it becomes impossible to suggest an accurate obstetric prognosis on the characters of the fore pelvis alone. If such a fore pelvis possessed a gynecoid or anthropoid posterior pelvis, delivery from below might be advised due to the compensation present in the long iliac portion and the broad sacrosciatic notch. But if the posterior pelvis displayed a short posterior iliac portion and a narrow male sacrosciatic notch (android), the fetal head would probably fail to engage.

Hart[11] in 1916 observed these principles but failed to stress their importance. He noted that "There are two major varieties of inverted pelves—the iliosacral and the ischiopubic; the former being the common one, the latter much more rare.

"The iliosacral: Here the deformity is at the brim and such a pelvis requires pubiotomy or cesarean section. . . . In the ischiopubic variety the ischium and pubes are male, and the ilium and sacral, female; thus the pubic arch is male and the intertuberosity diameter markedly diminished; as the ilium and sacrum are female, the former having a large sacrosciatic notch, the real labor hindrance is at the outlet and is formidable."

Hart's "iliosacral" type compares favorably with our "android" form and his "ischiopubic" pelvis compares with our "gynecoid" type with a narrow outlet. But we believe the latter terminology more concisely combines anatomical principles and obstetric significance.

* * * * *

OBSTETRIC SIGNIFICANCE

Platypelloid Type, Fig. 17, A.—The fetal head must engage in the transverse diameter of the pelvic inlet. Unless the subpubic angle is narrow with infringement of the ischial spines on midpelvic space, the

transverse diameter is the most ample diameter throughout the pelvis. The head should be allowed to descend in this diameter to the pelvic floor. If assistance by forceps becomes necessary, rotation must not be attempted until during that rotation the caput may be "taken up" in the outlet. The reason is obvious. Unless the occiput can escape into the outlet, the long diameter of the fetal head will be forced to occupy the narrow anteroposterior diameter betwen the unyielding symphysis in front and the sacrum behind. Two possible injurious results may follow, namely, serious intracranial injury to the child, or separation of the symphysis. Both these undesirable complications have been observed in the few samples of this rare pelvic form which we have had an opportunity to study.

The Android Type, Fig. 17, B.—This is the most dangerous form of pelvis that we have encountered. If the head engages in the transverse position, the prominent sacrum and narrow posterior pelvis force it forward into the narrowed anterior portion. In order to utilize the available space, it must assume the posterior position, and so permit the smaller frontal diameter to adapt itself in the narrow anterior portion of the inlet. Since there is a general convergence of the four walls of the pelvis toward the outlet, the head meets with increasing resistance as it descends. In the larger forms of this type, midpelvic arrest occurs in the pelvis where forceps are difficult to apply, and version and breech extraction is equally dangerous. If the extreme forms are identified before the onset of labor, elective cesarean section can be sanely advised. A wide subpubic angle compensates for the narrow sacrosciatic notch and forward sacrum and improves the prognosis.

The Gynecoid Type, Fig. 17, C.—The obstetric significance is chiefly limited to the small generally contracted form. This pelvis usually occurs in women of small stature and the babies as a rule are small. If engagement occurs, delivery can usually be effected by the vaginal route as relative ampleness exists throughout the true pelvis. If the head fails to engage, relative disproportion exists and cesarean section becomes the procedure of choice.

The presence of a narrowing of the subpubic angle may cause difficulty in the engagement of the fetal head under the symphysis and arrest may occur. But compensatory space exists in the posterior pelvis so that the obstetric significance is not great. Anterior positions are the rule in this pelvic type.

The Anthropoid Type, Fig. 17, D.—Depending upon the degree of contraction of the transverse diameter of the superior strait, the average fetal head may not engage in the transverse diameter and will be found riding high at term. Engagement is possible only in the anteroposterior diameter, as compensation exists in the posterior pelvis, the anterior part of the inlet being narrow. A small baby will frequently come through.

But, if it passes the inlet in the posterior position, difficulty in rotation of the head can be expected. If this pelvic type is recognized, the obstetrician may find that delivery can be effected with greater ease by

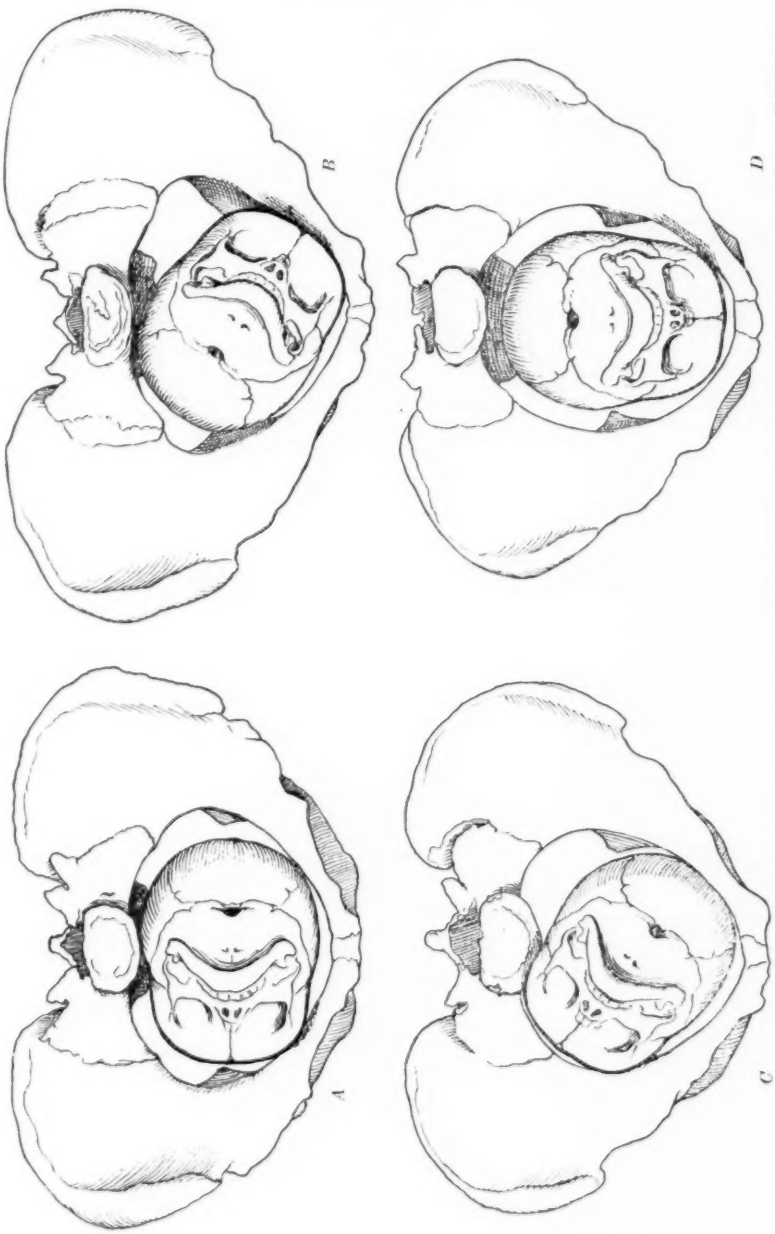


Fig. 17.—Diagrammatic representation of the engagement of the fetal head in the inlet. *A*, In the platypelloid type; *B*, in the android type; *C*, in the gynecoid type; *D*, in the anthropoid type.

delivery of the head with forceps in the persistent posterior position. It is mechanically wrong to attempt the rotation of the fetal head from a wide diameter through a narrower one.

The same principle holds in delivery of the aftercoming head in a version and breech extraction. Unless care is exercised, the head will be arrested in the narrowed transverse if it is allowed to enter it in the transverse position. Therefore, it is logical to rotate the head to a posterior or anterior position in the inlet itself, if this may be possible. It also must be remembered that the soft parts, flaring over the pelvic brim, further decrease the already constricted transverse diameter. In the extreme forms, particularly when narrowing of the subpubic angle exists, the head fails to engage and cesarean section becomes the usual method of delivery. In cases with a wide outlet rotation can usually be accomplished manually. But even when compensation exists in the outlet, if difficulty in rotation occurs, the obstetrician would be advised to deliver the head in the posterior position.

The following dictum describes the principle of engagement of the fetal head in these pelvic types. "The fetal head in its descent attempts to adapt itself to that diameter of the inlet most suited for its reception. If arrest occurs and forceps become necessary to effect delivery, the fetal head must be made to pass through that pelvic diameter most suited for its reception."

PRACTICAL SUGGESTIONS TO ASSIST IN THE CLINICAL RECOGNITION OF THE PELVIC TYPES

* * * * *

Palpation of the subpubic angle gives information regarding the character of the rami. Straight rami of the male type will grip the examining finger as narrowing exists under the symphysis. The presence of a Norman arch effect infers ampleness in this region. Although a narrow subpubic angle is present, the intertuberous diameter may reach normal dimensions. This, as mentioned before, is caused by the increased depth of the true pelvis (Fig. 12). The intertuberous diameter should be palpated deep posteriorly to avoid an erroneous measurement as the examiner may inadvertently measure from points higher on the pubic rami. The great width of the symphysis, 7 cm. or more, noted clinically in "masculine" forms, frequently is caused, not by an increase in bony width, but rather by the taut wide subpubic ligament and by the strong ligaments stretching between prominent pubic tubercles. Although these points lead to the clinical recognition of male characters in the fore pelvis, it is to be recalled that the absolute pelvic type depends on the shape of the inlet. Even in the presence of marked male characters in the pubis or ischium, compensatory space may exist in the inlet or posterior pelvis and the obstetrician must definitely note these points, aided by a roentgenologic examination if necessary, before he can accurately suggest the correct obstetric prognosis.

The capacity of the posterior aspect of the pelvis is best estimated by rectal or vaginal examination (Fig. 18). In our hands this method has proved to be a valuable diagnostic precedure. The examining finger locates the ischial spine and follows the most prominent part of the ligament to its insertion along the lower lateral border of the sacrum. A short ligament, two fingers or less in length, suggests two possibilities. If the sacrum has a normal curvature, a brim abnormality with a male sacrosciatic notch and short iliac portion is almost certain to be present. On the other hand, the sacrum may curve forward in its distal segments. The examiner as a rule can differentiate the two conditions by further palpation of the lower sacrum.

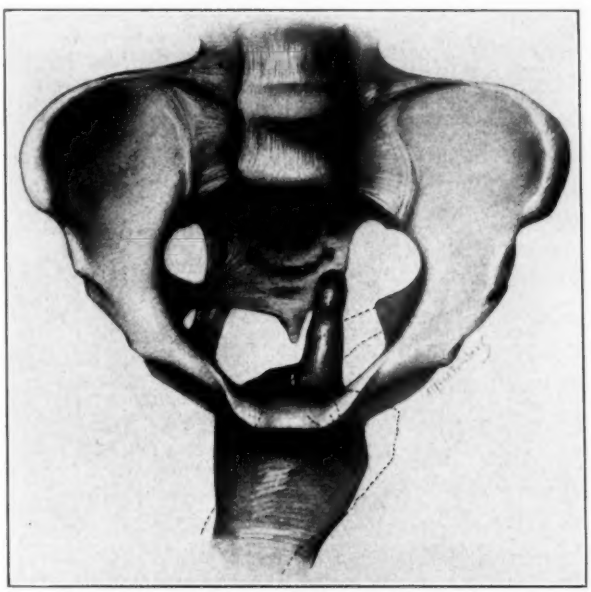


Fig. 18.—Rectal or vaginal examination of the distance between the lower lateral border of the sacrum and the ischial spine. In the living subject this distance is bridged by the sacrospinous ligament. If the sacrum has a normal curvature the length of the ligament is a good index of posterior pelvic capacity.

A long ligament may suggest two different inlet variations. If the sacrum is straight and flares backward, a narrow male sacrosciatic notch may be present, particularly if the promontory can be reached. If the promontory cannot be felt, a long sacrospinous ligament strongly suggests a long posterior iliac portion, a broad sacrosciatic notch and, hence, an anthropoid type.

We have observed that a decrease in the anteroposterior diameter clinically results in the diagnosis of the simple flat pelvis of other classifications. This is a very rare type, and by checking clinical findings with an x-ray examination, the majority of such cases are found to be android (masculine) forms.

SUMMARY

Examination of large series of skeletal material shows that pelves, on the basis of morphology, tend to segregate themselves into groups bearing certain common architectural characteristics. Four major groups have been recognized. On analysis these groups differ sufficiently anatomically to warrant a new classification of pelves.

The first group consists of an average form which in respect to the form of the compact pelvis displays the accepted sexual characters attributed to the female sex. This has been designated the "gynecoid" type of pelvis.

The second group appears to contain certain features common to the average male pelvis. These pelves are termed "android" types.

The third group in many respects bears a resemblance to the pelvic form of the great apes. The term "anthropoid" has been proposed for this special type.

The last group is characterized by a broad flat form similar to the simple flat pelvis of other classifications. It is a rare type and bears no resemblance to the great apes or other lower forms. The term "platypelloid" originally proposed by Turner,[18] seems descriptive and satisfactory for classification purposes.

These variations in female pelves are not associated with or caused by pathologic processes. The more extreme forms have been long recognized by anatomists, anthropologists, and obstetricians. We have attempted to correlate these observations in order to facilitate the application of this anatomical knowledge to the mechanism of labor.

The rôle played by these pelvic types in relation to ease or difficulty in labor is briefly discussed.

* * * * *

A few practical suggestions in regard to their clinical recognition and slight modifications in the method of visualization of the pelvis by means of stereoroentgenograms to aid in their identification have been offered.

We wish to acknowledge our indebtedness to Professor B. P. Watson and Staff at the Sloan Hospital for Women; to Dr. Dudley J. Morton of the Department of Anatomy, College of Physicians and Surgeons, Columbia University; and to Dr. Paul C. Swenson of the Department of Roentgenology, Presbyterian Hospital, for the interest and cooperation extended throughout this investigation.

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GRANULOSA CELL OVARIAN TUMORS AS A CAUSE OF PRECOCIOUS PUBERTY, WITH A REPORT OF 3 CASES*

EMIL NOVAK, M.D., BALTIMORE, MD.

(From the Gynecological Department, Johns Hopkins Medical School)

THE total number of cases of precocious female puberty reported in the literature is still well below 200, so that it must be looked upon as one of the rare conditions encountered by gynecologists or pediatrists. Moreover, many of these reported cases emanate from the very old literature, dating as far back as 1658, when Mandeslo[1] described such a case. Any attempt at reanalyzing these older cases in the light of our newer knowledge of endocrinology is worthless, for most of them were reported simply as medical curiosities, with usually little or no pathologic data upon which to base a reappraisal.

One of the most exhaustive collections of these cases, going back into the very old literature, was made by Lenz[2] in 1913. A study of the tabulated summary which he includes in his paper is of great interest, but has the serious disadvantage that in most instances one can only speculate as to the etiology of the 130 cases thus collected, for, in the then existing state of our knowledge, there could be no intelligent division of cases on an etiologic basis. The tabulation was almost purely a clinical one. In the entire series, postmortem findings are recorded in only 8, and these are usually of little value in drawing conclusions as to the probable nature of the underlying disorder.

While, therefore, a study of these older cases is of interest in a clinical sense, and in encouraging speculation as to their probable etiology, it is upon the more recently reported cases that one must chiefly depend for suggestions as to the general causes underlying the premature development of puberty changes, or *Pubertas praecox*. Lenz himself draws a rather sharp line between three categories of cases, viz. (1) *Menstruatio praecox,* in which the premature inauguration of the function is the sole manifestation; (2) *Pubertas praecox,* in which premature menstruation is associated with a precocious development of such secondary sex characters as mammary growth, development of the external and internal

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sex organs, hairy growth on the genitalia and in the axillae, etc. (3) *Evolutio praecox,* in which, in addition to the above mentioned changes, there is evidence of precocious somatic and osseous growth. While such a division is attractive, its value is doubtful, for it obviously represents a confusion and mingling not only of grades but also of etiologic types.

Endocrine Causes.—We know little enough even now of the causes of precocious puberty, or even of the underlying causation of the normal pubertal phenomena, and yet certain etiologic factors appear to have sifted out as definitely related to the abnormally early appearance of puberty phenomena. These pertain to the various endocrine structures, and especially to the pineal, suprarenals, and the gonads.

In view of the admittedly dominating rôle of the anterior hypophysis over the function of the gonads, it seems strange that it has so rarely been incriminated in the etiology of premature puberty. Indeed, with the exception of one or two doubtful cases, I can find no instance of this syndrome in which a lesion of the anterior lobe has been established as the cause. This in spite of the fact that most authors incline to the view that it is in the anterior lobe that the machinery of female cyclical activity is set in motion, and that in later life the female sex hormone secretion is dependent upon the functional activity of the hypophysis.

The pineal body, concerning whose function we know practically nothing, is occasionally the seat of tumors, especially teratomas, which have in some cases been associated with premature developmental changes, though not usually involving the sex apparatus. Furthermore, in almost every recorded case (all except 2 of 70 cases, according to Engelbach[3]) such syndromes have involved males rather than females, so that one does not frequently have to take it into consideration in searching for the cause of female sex precocity.

As to the suprarenals, there can be no doubt as to their relationship with sex function, as might be expected from their embryologic development from the mesoderm of the wolffian body, in intimate contiguity with the sex gland area. It has long been known that tumors of the suprarenal may bring about the most profound developmental changes. In the adult female these commonly take the form of masculine hirsutism, with the development of a heavy growth of hair on the face, abdomen, chest, and extremities. Other evidences of masculinization may appear, such as marked hypertrophy of the clitoris, and loss of the feminine contour of the body, with the development of the more angular masculine outlines. Amenorrhea is the common gynecologic symptom. I shall not stress this adult syndrome further, except to call attention to its similarity and probable relation to that produced by certain masculinizing tumors (arrhenoblastomas) developing in the medulla of the ovary.

Tumors of this latter group are now believed to arise from undifferentiated cells persisting in the region of the rete ovarii, which is to be looked upon as the homologue, in the female, of the male testis. For

the clarification of this subject we are indebted chiefly to the studies of Robert Meyer.[4] These indifferent cells are capable of developing along either male or female lines, so that tumors originating from them may develop masculinizing endocrine potency, bringing about profound changes in the sex characters of the patient. For a fuller discussion of these tumors, and of their relation to the general problem of sex differentiation and intersexuality, I may refer to the publications of Meyer, and to a forthcoming paper by Long and myself,[5] to be presented at the coming meeting of the Section on Pathology and Physiology of the American Medical Association.

When suprarenal tumors, usually adenomas or hypernephromas, develop in young children, they bring about a remarkable acceleration of somatic overgrowth, together with a precocious development of the sex organs, especially the external group. In the female, marked hypertrophy of the clitoris may occur, or, at times, a pseudohermaphroditismus externus. Premature menstruation, however, occurs in only a minority of cases, though hypertrichosis is common. The striking feature of such children, however, is the rather massive overgrowth of the muscular and osseous systems, or, for that matter, of the entire soma, so that the condition is very appropriately spoken of as macrosomia, or macrogenitosomia *(macrogenitosomia surrenale)*. It is this general overdevelopment of the "infant Hercules" type, that most often gives the clue to the suprarenal source of the disturbance. The disappearance of the abnormal symptom in a few cases where the tumor could be removed would appear to confirm its etiologic responsibility. In other cases no tumor can be found, though hyperplasia of the suprarenal cortex may be present. In such cases there is always the possibility of the pituitary being the primary seat of the disorder, for in acromegaly and other hyperpituitary states, the finding of cortical adenoma or hyperplasia is common, presumably secondary to the pituitary disorder.

It is with ovarian tumors, however, that we have most to do when we consider the etiology of female sex precocity. Many types have been described in past reports of cases of this character, such as carcinoma, sarcoma, teratoma, cystadenoma, etc. In Elterich's review[6] of 25 cases of precocious puberty in which a pathologic report was given, no less than 21 were found to be due to an ovarian tumor of some sort. It is suggestive that not a few of these pathologic reports mention that the tumor was of "unusual" or "puzzling" type, and it is highly probable that a review of all the pathologic material would show that a large proportion of these cases belongs in the common category of granulosa cell tumors. I say this partly on the basis of our own experience, for, as will be seen, the tumors found in my own cases had been originally misdiagnosed, two of them having been observed before the granulosa cell tumor had achieved general recognition as a pathologic entity. This has been the experience of other laboratories as well.

Granulosa Cell Tumors.—This is not the place to review the clinical and pathologic characteristics of this type of ovarian tumor in extenso. For such a discussion I would refer the reader to the papers of Meyer,[7] Neumann,[8] Habbe,[9] Klaften,[10] and TeLinde,[11] and also to the forthcoming paper by Novak and Long.[5] Suffice it to say that this neoplasm develops from granulosa cell rests ("Granulosaballen"), which, as Meyer believes, are left over from the formation of the follicular apparatus. That such rests actually exist may at times be demonstrated microscopically, especially in the ovaries of young children. Tumors arising from such granulosal tissue, already differentiated along female lines, have the capacity of hyperfeminizing the patient, for the constituent cells retain the physiologic function of producing the female sex hormone. This fact explains their characteristic symptomatology.

They occur most often in elderly women, and, under such conditions, they bring about an apparent return of the menstrual function, or, at any rate, of more or less periodic bleeding. The uterus is increased in size, and its mucosa not infrequently shows marked hyperplasia, similar to that seen in the so-called functional uterine bleeding of younger women, also due to relative excess of the female sex hormone.

Only a few cases have been observed in children, and here, as might be expected, the symptoms are even more striking than in older women, where sex characters are already well established. The important rôle of the female sex hormone in the differentiation of the female sex characters is now generally accepted. A great excess of this hormone in the young child would be expected to precipitate the changes commonly occurring at puberty, and this is exactly what occurs.

There have previously been reported only 3 cases of precocious puberty in which the etiologic rôle of the granulosa cell tumor has been clearly established, although there is not the slightest doubt that a considerable number of others have been incorrectly reported under other designations.

The first case in the literature is that of Blau.[12] The clinical picture was quite characteristic, and the microscopic sections, as pictured in his paper, leave no doubt as to the nature of the ovarian tumor. This patient was five years old.

The second case of this type was reported by Meyer, and is again summarized in Habbe's recent report[9] of 33 cases of granulosa cell tumor observed in Meyer's laboratory. The patient was five years old, and in addition to menstrual bleeding, showed marked mammary hypertrophy. The tumor was bilateral, the left ovary being removed, while a small portion of the right was conserved. The bleeding and the breast overgrowth disappeared, but returned three years later, at which time a recurrence of the tumor was found to have occurred in the portion of the right ovary which had been retained. A second operation was again followed by disappearance of the abnormal manifestations, and the patient was well ten years later.

The impressive feature of this case is the clear demonstration which it gives of the etiologic rôle of the ovarian tumor in the production of the syndrome. The disappearance of symptoms after removal of the tumor, their reappearance with

recurrence of the growth, and their final disappearance after the second operation would seem to establish the hormone function of the tumor beyond all doubt. The case reported by Rummeld[13] (1931) is obviously the same as that observed by Meyer, who had made the pathologic study of the tumor from Rummeld's patient.

The third case, published by Pahl[14] in 1931, concerned a patient of nine years, in whom the characteristic symptoms of vaginal discharge, with later bleeding, mammary hypertrophy, and the growth of pubic and axillary hair, were all present. The left ovary was replaced by a cystic tumor the size of a man's head, but the uterus was not appreciably enlarged. The tumor was a granulosa cell carcinoma, with marked evidence of degeneration.

To the 3 cases already reported in the literature in which granulosa cell tumors were associated with the clinical syndrome of precocious puberty, I can add 3 more. Two of these cases have been previously reported by others, as instances of premature puberty, associated with ovarian tumor, although the real nature of the latter was not recognized at that time. Since then I have had an opportunity of studying sections from these tumors, and both are typical granulosa cell neoplasms. It, therefore, seems worth while to re-report the cases, briefly at least, under the proper category, and to add the third case, as yet unreported.

CASE 1.—For the privilege of including this in my report, I am greatly indebted to Drs. Clarence B. Ingraham and Chesmore Eastlake, of Denver, Colo. The case was reported by Dr. Eastlake in *Colorado Medicine* in September of 1931,[15] although at that time the tumor was believed to be an "embryonal carcinoma."

The patient was seen at the age of three years, eleven months, and at that time she had menstruated regularly for four months. Physical and mental development were normal until a few months before the onset of the menstrual function, when she grew rapidly, so that when she came under observation, she was as tall as the average child of seven (Fig. 1). The breasts showed marked hypertrophy, axillary and pubic hair appeared, and the external genitalia assumed the pubertal type. The abdominal examination disclosed a freely movable mass in the left lower quadrant, and, on rectal examination, this was considered to be a tumor of the left ovary.

This was confirmed at operation, which was performed by Dr. Ingraham. A tumor of the left ovary was revealed, measuring 3.5 by 2.5 by 2.5 inches. At the time of operation it was thought to be a sarcoma. An extract of the tumor was at once prepared by Dr. Gustafson of Denver University, and later examined by Dr. Robert T. Frank, who reported that "it showed some activity which signifies that the tumor elaborated female sex hormone."

The patient promptly recovered, and in two years there has been a complete recession of the abnormal manifestations. Dr. Eastlake tells me that her present condition is that of any normal child of her age.

The pathologic examination of this tumor was made possible to me through the kindness of Dr. Ingraham, who brought a slide with him to our last Hot Springs meeting in 1931. There seemed no doubt that the tumor was of the granulosa cell variety, and this diagnosis was confirmed by Prof. Robert Meyer, who was our guest at that meeting.

Microscopic examination showed a granulosa cell tumor of the diffuse type (Fig. 2). It was made up of cells which varied considerably in shape and size. Most of them were round or oval, with large, rather pale and slightly granular nuclei. Some of the cells were spindle-shaped, with darker, more elongated nuclei.

No mitoses were observed. In many places the cells showed a tendency to grouping in short strands or tubules, which on cross-section presented as tiny circular clumps of cells. As only one section was available for study I do not know whether other pictures were present in other parts of the tumor, but there can be no doubt of the granulosal nature of the tumor.

Fig. 1.

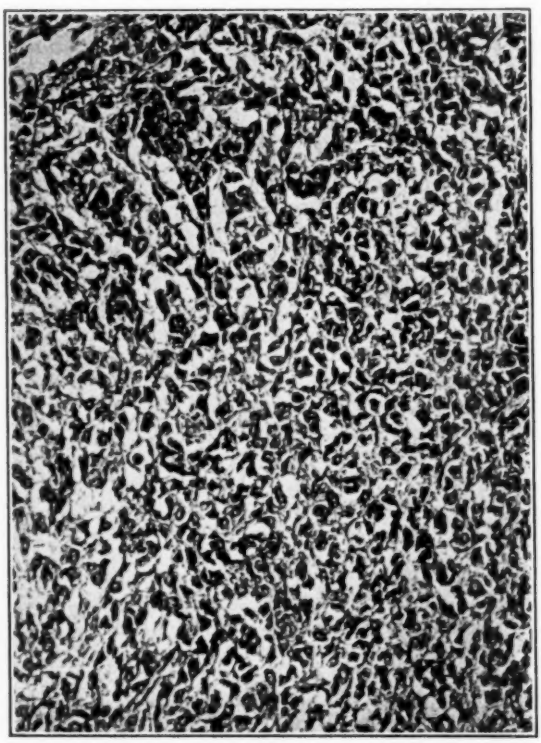

Fig. 2.

Fig. 1.—Lateral view of patient (Case 1) at age of three years and eleven months. Note especially the hypertrophy of the breasts. Menstruation had begun at three years and seven months (courtesy of Dr. Chesmore Eastlake, Denver, Colo.).

Fig. 2.—Granulosa cell tumor from Case 1 (see text).

CASE 2.—This case was met in the course of a resurvey which we have recently been making of the ovarian tumors in our laboratory material. Like the first, this had likewise been reported, but only as an instance of ovariotomy in a young child, with no stress upon the premature developmental changes obviously disclosed by the history. The tumor was reported at the time[16] (1905) as an adenocarcinoma.

The patient was first seen in the out-patient department on Oct. 8, 1904, when she was five years old. At that time the complaint was of a vaginal discharge. There was a history of frequent attacks of abdominal pain, occurring over a period of one and a half years, and following shortly after a severe fall at the age of one and a half years. Later the attacks became only occasional. Two months before admission to the dispensary a swelling of the abdomen was noticed, and about a month later a "whitish, offensive vaginal discharge."

When seen again on Oct. 23, 1904, the mother reported that eight days previously the discharge had become bloody. At this time a hard rounded abdominal mass was felt, extending to the umbilicus. "Both mammae were very large for a child of

that age," and "pubic hairs were well developed." The patient was admitted to the hospital. Unfortunately, no photographs were made of this patient.

Examination under anesthesia showed what was apparently a tumor of the left ovary, and this was thought to be an ovarian cyst.

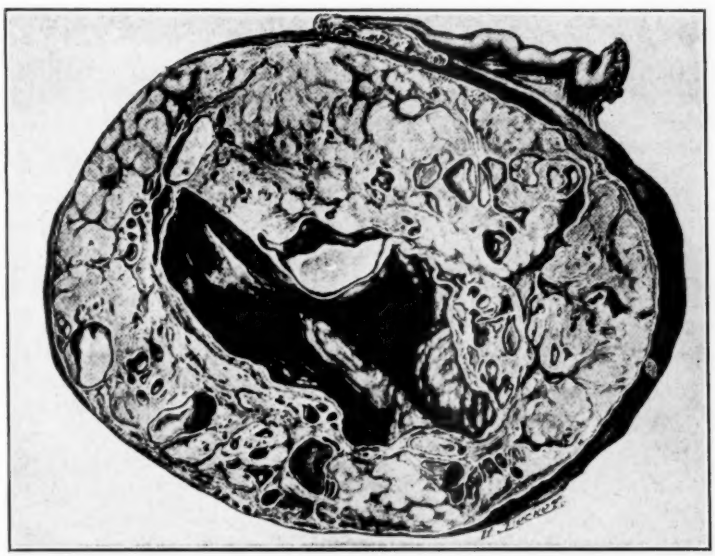

Fig. 3.—Gross appearance of tumor of left ovary removed in Case 2.

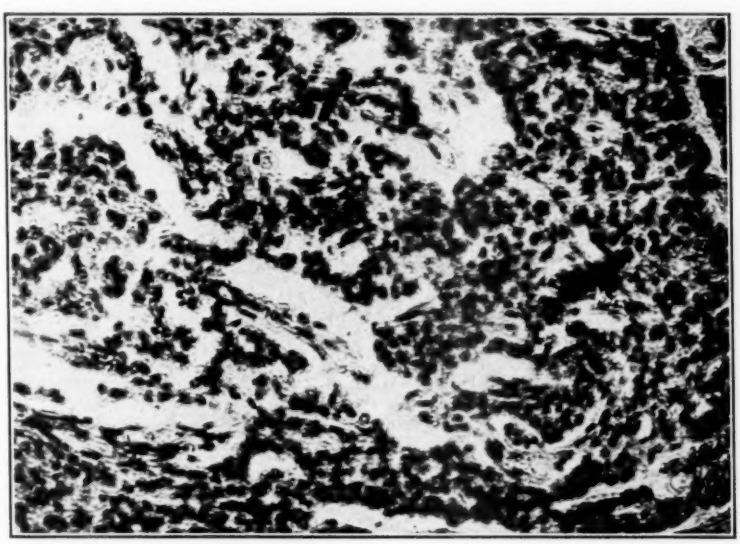

Fig. 4.—Microscopic appearance of tumor in Case 2. It is a typical granulosa cell tumor of the diffuse variety.

At operation a left ovarian tumor was found, measuring 12.5 by 8.5 by 7 cm. (Fig. 3). It was of greenish blue tinge, with here and there brownish beefy areas showing through the glistening surface. On cut surface it showed a definite capsule, from which extended connective tissue trabeculas which divided the mass into irregular lobules. The tumor substance was grayish and granular in appearance.

Near the center was a cystic cavity 7 by 5 by 4 cm. in diameter, and several smaller cysts were seen between this and the circumference of the tumor. These measured about 1.5 cm. in diameter.

Microscopically, this tumor presented in most places a pattern not unlike that seen in Case 1, with the same rather diffuse structure of round or oval cells with rather large pale nuclei (Fig. 4). Only an occasional mitotic figure was noted. Near the periphery of the growth, however, there was a rather sharp transition in pattern, for here the cells are arranged in strands and tubules (Fig. 5), often rather convoluted. The epithelium has a tendency to be arranged in a palisade-like fashion, the long rows of cells being strikingly uniform. Here we are apparently dealing with a transition to the cylindroma-like pattern so common in many granulosa cell tumors.

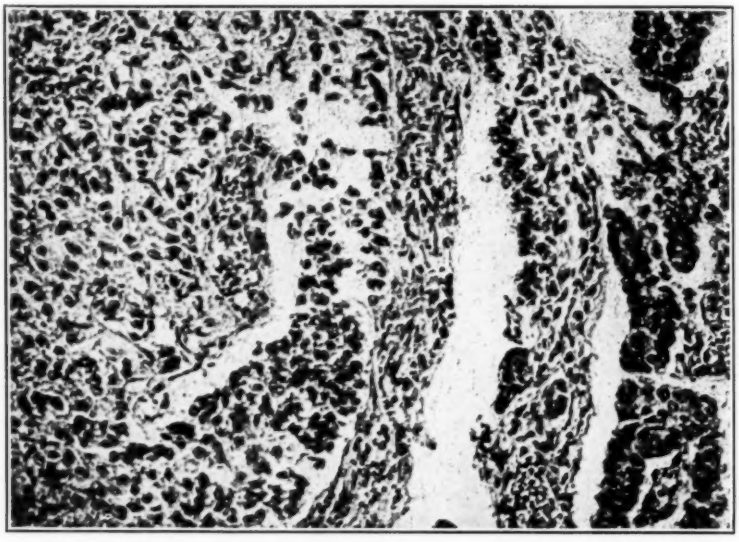

Fig. 5.—Another area in tumor. Case 2, showing a transition to the cylindromatous pattern so often seen in granulosa cell tumors.

CASE 3.—For the privilege of including this case in my report and also for the accompanying photographs I am extremely grateful to Dr. Edwards A. Park, director of the Harriet Lane Home for Children of the Johns Hopkins Hospital. The patient, a colored child of six years, first came under observation on July 16, 1915. She had had an attack of vaginal bleeding four weeks previously, supposedly following a fall. This had been free for three days, but there had been slight staining since then.

Physical examination at this time showed the general development of an adult woman. The breasts were very large, and there was a heavy growth of axillary and pubic hair, the hair being about 4 inches long. The hymen was complete, but "looked as if it might have been injured."

The patient returned on April 24, 1916, with a history of having menstruated for one week in September, 1915, again for one week in December, and again for a few days in March, 1916. Menstruation had again recurred on April 23. At this time the patient was seven years old, weighed 55½ pounds, and was 50 inches tall.

The secondary sex characters were those of an adolescent girl. She was heavily built, with broad pelvis and hips. Axillary and pubic hair growth were

heavy, the external genitalia were of mature type, and the clitoris was long (Fig. 6). There was a milky discharge from the vagina, and this was negative for gonococci. The breasts were very large, as seen in Fig. 7. The breasts measured 10 cm. in diameter, with abundant glandular tissue. The nipples were well marked, erectile, measured 5 mm. in length, but no secretion could be expressed. Abdominal examination at this time revealed a hard, somewhat nodular mass extending from the pelvis to within about 1 inch of the umbilicus. It was quite freely movable in the arc of a circle whose center was apparently in the right side of the pelvis. The patient was apparently below normal mentally, and of uncooperative demeanor.

At operation a tumor of the right ovary, about the size of a child's head, was found (Fig. 8). The right tube and ovary were removed. The uterus showed

Fig. 6.

Fig. 7.

Fig. 6.—External genitalia in Case 3. Note the well-developed labia, the heavy growth of hair on the mons and labia majora, and the large clitoris.

Fig. 7.—Showing the marked general development, the mammary overgrowth, and the broad hips of patient in Case 3 (aged six). There is a heavy growth of axillary and pubic hair, though this is not clearly brought out in the picture.

marked hypertrophy, measuring 12 cm. from the top of the fundus to the lip of the cervix, and 9 cm. from the same point to the internal os. It was 5.5 cm. in diameter at its widest point. The left tube and ovary were normal, the latter measuring 1.5 by 1.5 by 3 cm. No corpora lutea were seen. The adrenals were palpated and found normal. The patient made an uneventful recovery. She was seen again one year after the operation. There had been no further bleeding, the breasts were very much smaller, but the axillary and pubic hair growth was still present. The uterus had shrunken to normal size, and no abnormalities were palpable in the sides of the pelvis.

The tumor of the right ovary was somewhat heart-shaped, and measured 7 by 11 by 12 cm. Its peritoneal surface was smooth. At one pole was the mesosalpinx, together with a greatly hypertrophied, but otherwise normal tube and ovary, from the upper pole of which the tumor arises. There is a dark brown area of hemorrhagic discoloration, about 7 by 4 cm., at one pole of the tumor. On section, the upper half of the tumor is seen to have undergone cystic change, there being two large cysts, each about the size of a hen's egg, together with a number of

Fig. 8.—Tumor of right ovary removed in Case 3.

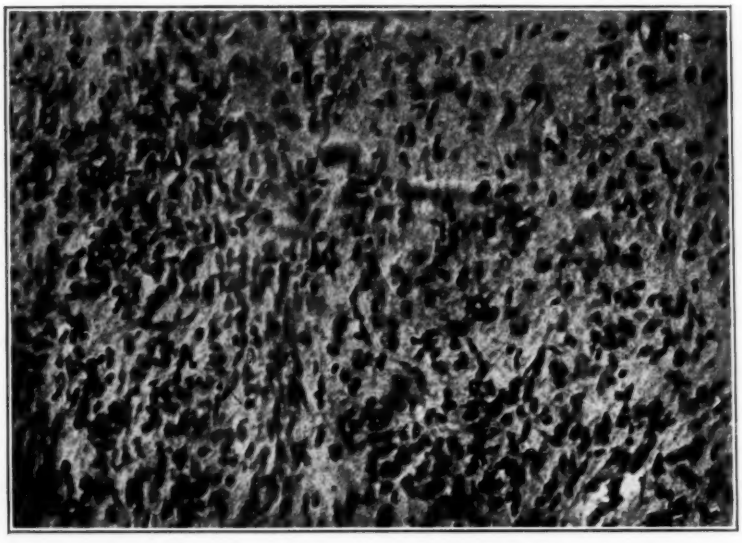

Fig. 9.—Granulosa cell tumor, of diffuse type, from Case 3.

smaller ones. The remainder shows a rather dense trabeculation of fibrous tissue, the tissue between the septa being soft and granular in appearance.

Microscopically, the tumor is seen to be of the diffuse granulosa cell variety. The cells vary somewhat in shape and size, as do the nuclei, but the characteristic clump-like and strandlike arrangement seen in most places leaves no doubt as to the diagnosis (Fig. 9).

CLINICAL FEATURES

The syndrome presented in these cases is strikingly uniform. In most cases the first symptom is a whitish vaginal discharge, often periodic, giving way later to a periodic bleeding. This is often somewhat ir-

regular at first, as with the normal girl at puberty, but later becomes quite regular. There may be some whitish discharge between the periods. Skeletal growth may show marked acceleration. Mammary hypertrophy is an early manifestation, the breasts becoming full, rounded, and firm, and the nipples becoming prominent. The swelling of the breasts may become more marked at the time of the periodic discharge or bleeding. Pubic and axillary hair soon appear, and the external sex organs may resemble those of the girl at normal puberty. The uterus is always increased in size, and its contour is like that of the pubertal organ. Examination of the blood and urine may show the presence of folliculin. If, in a patient with such symptoms, an ovarian tumor is revealed by examination, it is almost certain to be of the granulosa cell variety.

PATHOLOGIC VARIATIONS AND MALIGNANCY OF GRANULOSA CELL TUMORS

There are many individual variations in the pathologic structure of such neoplasms. Some belong to the type designated as folliculoma ovarii (von Kahlden type), though more frequently they are of the nonfolliculomatous variety, this embracing such terms as diffuse, cylindromatous, sarcoma-like, etc. Different portions of the same tumor may present different pictures. It is not uncommon to see sections which cannot be distinguished from sarcoma, or which to all intents and purposes are sarcoma, though other parts may reveal the more characteristic finely folliculoid or strandlike picture.

If one accepts the newer teaching of Fischel[17] and others as to the development of the follicular apparatus from the ovarian mesenchyme rather than from the germinal epithelium, as had been believed, there is no incongruity in believing that the cells of certain sarcomas of the ovary may possess endocrine functions and produce folliculin. The ovarian tumor which, in the past, has most often been reported as a cause of precocious puberty, is sarcoma. Hence the pertinence of this observation. Furthermore, some of these ovarian sarcomas would undoubtedly show, on more careful study, the characteristics of granulosa cell tumors, even from a purely pathologic standpoint.

While granulosa cell tumors are commonly classed as carcinomas, their degree of malignancy is usually slight, so that recurrence after removal occurs rather infrequently. In about 6 or 7 reported cases, all in adult women, the tumors have shown a high degree of malignancy. In one of our recent cases, extensive peritoneal recurrence followed within three months of hysterectomy, with bilateral salpingo-oophorectomy, performed for an ovarian tumor of this sort. Such tumors, however, give microscopic evidence of their malignancy in the marked evidence of anaplasia shown by the tumor cells, while such changes have been much less striking in most of the tumors we have examined.

Indeed, it would seem that a distinction could appropriately be made between granulosa cell carcinoma and granulosa cell adenoma. The term adenoma is rather generally employed in the designation of corresponding benign tumors of the endocrine organs, especially the pituitary and the suprarenal, even though such tumors often fail to show any very distinctive gland pattern, so that its extension to these essentially benign ovarian tumors would seem proper.

THE OCCURRENCE OF PREGNANCY IN CASES OF PRECOCIOUS PUBERTY

In a considerable number of instances patients with precocious puberty have become pregnant at abnormally early ages.

Perhaps the best known of these is the often cited case of Anna Mummenthaler, reported by Albrecht Haller[18] in 1751. This patient began to menstruate at the age of two, having shown unusual development at birth, together with a growth of pubic hair. At the age of nine she gave birth to a dead child. She continued to menstruate until fifty-two years of age. Even more remarkable is the first case reported in the literature, as far back as 1658, by Mandeslo,[1] whose patient began to menstruate at three, and gave birth to a son at the age of six. According to Elterich, at least 30 cases of precocious pregnancy have been recorded.

It is obvious, however, that pregnancy can occur only where ovulation is taking place, and that the latter is not the case with granulosa cell tumors alone. These bring about an excessive production of folliculin, but do not, unless our ideas of physiology are all wrong, cause ovulation. When the maturation and rupture of follicles is observed, with corpus luteum formation as a result, it seems necessary to invoke the agency of the pituitary, for it is the anterior hypophyseal lobe which is now accepted as the "motor" of the ovary in this regard. This need not necessarily indicate the presence of a hypophyseal tumor, for a review of the reported cases does not bear out this view. As a matter of fact, it would seem that, in a certain proportion of cases, the endocrine forces set loose in cases of precocious puberty are exactly the same as those concerned in normal puberty, though why they should be released thus abnormally early is not clear.

To illustrate this last point, reference may be made to the history of the case reported by Lenz,[2] who had an opportunity of studying his patient over a period of many years. This child was born Nov. 8, 1897. At three months the breasts were well developed, and menstruation appeared at four months. Pubic and axillary hair growth were observed at one and one-half years.

Lenz's first examination was on March 1, 1904, when the patient was six years old. At this time she was 127 cm. tall and weighed 26.5 kilo., giving the impression of a child of thirteen. Her figure was of a mature type, the breasts were fully developed, and there was abundant pubic and axillary hair. She had been menstruating every twenty-eight days, the periods lasting three or four days. X-ray studies showed marked acceleration of bony development. The labia majora were large, fatty, and covered with hair, while the uterus was somewhat enlarged. The

rectal examination, moreover, showed the left ovary to be rather tender and enlarged to the size of a pigeon egg.

A second examination on June 28, 1905, showed the same general picture, as did the third on June 8, 1908. Menstruation was still quite regular, though the progression of the other symptoms was less striking, suggesting that the maximum had been passed at about the age of six. The swelling of the left ovary had disappeared. The last report, in 1912, indicated that the child was apparently quite normal, her weight being 49.3 kilo. and her height, 135 cm. Menstruation was still quite regular, the flow lasting two or three days.

A recent case of precocious puberty of our own, which I am not including in this report, presents many points of similarity to Lenz's case, and we believe it quite possible that a similar future course may be unfolded. In patients of this group, there is a sudden transition from infancy and early childhood to puberty and adolescence, so that childhood is either greatly abbreviated or entirely skipped. In Lenz's patient the maximum of developmental change was apparently reached at about the age of six, after which development, from a sex standpoint, remained at a standstill, as in the young woman who has reached full maturity.

There can rarely be any certainty of such a favorable future in any case in its early phases, for there is always the possibility that a tumor in one or other of the ductless glands, undiscoverable when very small, may make itself evident later on. It is this frequency of tumors which has the greatest bearing upon the patient's expectation of life, for a large proportion of patients have died at an early age because of the tumors or of operations for their relief.

PHYSIOLOGIC CONSIDERATIONS

The capacity of granulosa cell tumors, when developing in childhood, of bringing about premature pubertal phenomena is due to the fact that the tumor cells, like the normally functioning granulosa of the graafian follicles, produce folliculin, or female sex hormone. That this is actually true has been shown experimentally through the injection into castrated animals of extracts of tumor tissue, and by implantation studies. In our Case 1, Dr. Frank was able to demonstrate such a physiologic property of the tumor tissue.

That the male and female sex hormones are of great importance, in the higher forms of animals, in the differentiation of the secondary sex characters, is now accepted by all biologists. In the lower forms, such as the insects, the determining force apparently emanates entirely from the germ cells themselves, no endocrine mechanism being demonstrable. In the human being, however, the endocrines play a very important auxiliary rôle, although here, too, the initial impulse from the germ cell is of fundamental importance. Some at least of the biologic concepts concerned in this question have been discussed in the forthcoming paper by Long and myself,[5] already referred to.

The premature menstruation observed in cases of the type I have reported may be clinically identical with that observed during the reproductive epoch, and yet ovulation does not occur in cases of granulosa cell tumor. This is a very significant observation in view of the discussion as to the importance, or nonimportance, of ovulation to menstruation. More and more evidence is accumulating to indicate that regular periodic uterine bleeding, clinically not distinguishable from normal menstruation, may occur in the absence of ovulation or corpora lutea. Convincing evidence of this fact in the case of monkeys has been adduced by Corner,[19] Hartman[20] and Allen.[21] There is also abundant evidence to indicate that the bleeding of menstruation is dependent upon periodic drops in the folliculin blood content.

The same mechanism is undoubtedly concerned in the periodic bleeding seen with granulosa cell tumors, as when they occur in very young children or in women beyond the menopause. It may be freely conceded that the histologic changes in the uterus are quite different from those seen in the usual menstrual cycle, but, whether we speak of such periodic bleeding as menstruation or "pseudomenstruation," it is clinically identical with the genuine function. The significant thing is that, as I have said, it occurs without the agency of ovulation or corpora lutea, and it is apparently to be explained altogether by fluctuations in the folliculin level. Behind this there is of course to be considered the probable underlying rôle of the anterior hypophysis, but the discussion of this question would lead us too far afield.

Finally, it may be stressed that these granulosa cell tumors are illustrative of an increasing group of neoplasms, more particularly those arising in the ductless glands, which exhibit an active functional capacity. Other examples will at once suggest themselves, such as the eosinophilic pituitary adenomas so often producing gigantism or acromegaly, the basophilic hypophyseal adenomas concerned in the syndrome recently described by Cushing, the suprarenal adenomas or hypernephromas which are responsible for certain remarkable sex character abnormalities, the ovarian arrhenoblastomas already alluded to as bringing about amazing masculinization phenomena in the female, and a number of others which might be mentioned. No longer, therefore, can we look upon tumors as purely parasitic, nonfunctioning growths, for, at least in the case of those of endocrine gland origin, there is now definite proof of the correctness of the dictum enunciated many years ago by Bard[22] that "les cellules neoplastiques continuirent a produire leurs secretions physiologiques."

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26 East Preston Street

A YOUNG HUMAN OVUM OF THE EARLY SOMITE PERIOD*

Jennings C. Litzenberg, M.D., Minneapolis, Minn.

MOST young human ova are obtained by accident. Our ovum was discovered, fortuitously, in a uterus after hysterectomy for myomas. When the patient was admitted to the Minnesota General (University) hospital on April 5, 1932, her chief complaint was pelvic pain and a palpable mass in the lower abdomen. Her menstruation was overdue fifteen days. She declared that she had never skipped a period, except when pregnant.

The uterus was as large as a four months' pregnancy and contained many myomas of varying size. Because of the tumors it was impossible to elicit the usual signs of pregnancy, but on account of the history, a suspiciously soft area in the mass, and a softened cervix, we decided to await the result of the Aschheim-Zondek (Friedman) test of pregnancy before considering operation. The test was negative, so on April 8 a supravaginal hysterectomy was done, forty-seven days after the last menstruation, and approximately thirty-two days after ovulation. She, therefore, was, according to her history, in the fourth week of gestation.

Because of our previous suspicions, the uterus was cautiously opened immediately after its removal. A little above midway between the internal os and the fundus uteri, was a furrowed, domelike elevation of the decidua, two-thirds of which was on the posterior, and one-third on the left lateral wall of the uterus. To the right was a small myoma, but not encroaching upon the site of implantation. These facts probably account for the appearance of uterine muscle in the specimen (Fig. 1), not only at base, but on either side of our sections.

A block was removed, 5.3 cm. by 2.2 cm. by 2.4 cm., including the posterior muscle wall as the base, and the decidua capsularis as the apex. The block was immediately placed in 10 per cent formalin, dehydrated, and imbedded in paraffin in vacuo.

The specimen was cut in sections 8 microns thick, in a plane that gave us, in each section from above downward; the decidua capsularis, the implantation cavity, the chorionic vesicle, the decidua basalis, and the uterine muscle.

I anticipated that, on account of the immediate placing of the block in the fixing solution, we would be dealing with tissues fixed while living and before cell

*Read at the Fifty-Eighth Annual Meeting of the American Gynecological Society, Washington, D. C., May 8, 1933.

changes would occur. The tissues of the chorion and uterus were well preserved, but I was greatly disappointed to find a moderately degenerated embryo. However, it can be quite accurately studied. In all probability the embryo had perished before the operation. There was no yolk sac.

Age of the Ovum.—It is difficult to accurately determine the age of an early human ovum by the usual clinical history; however, in this case the estimated age and the embryologic development approximate each other rather closely. Authorities now agree that the most accurate in-

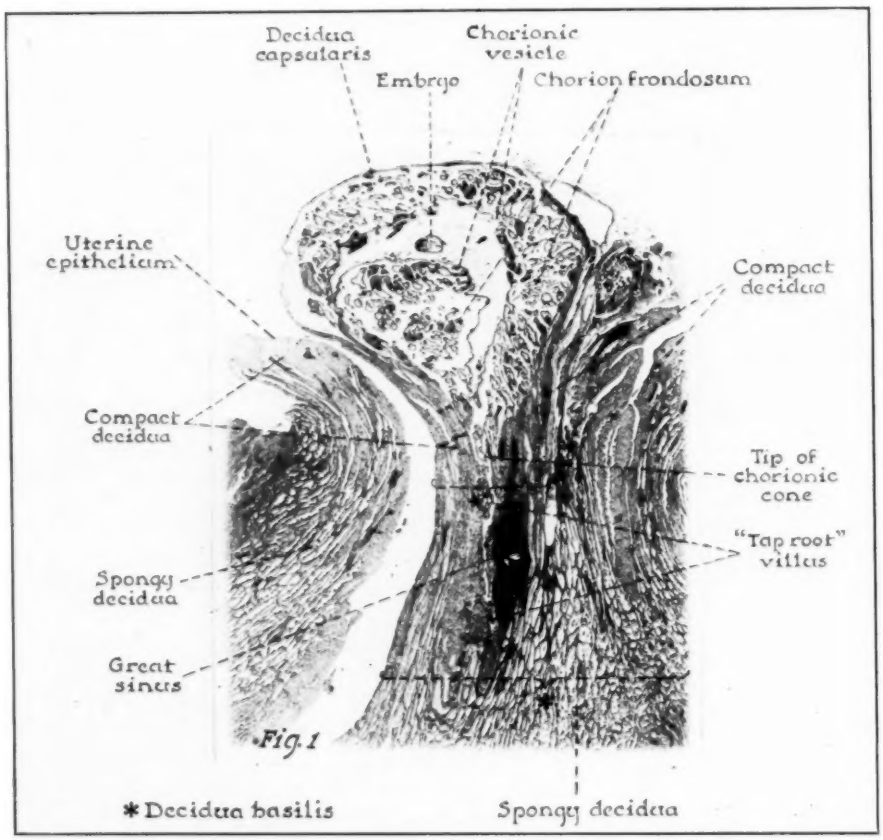


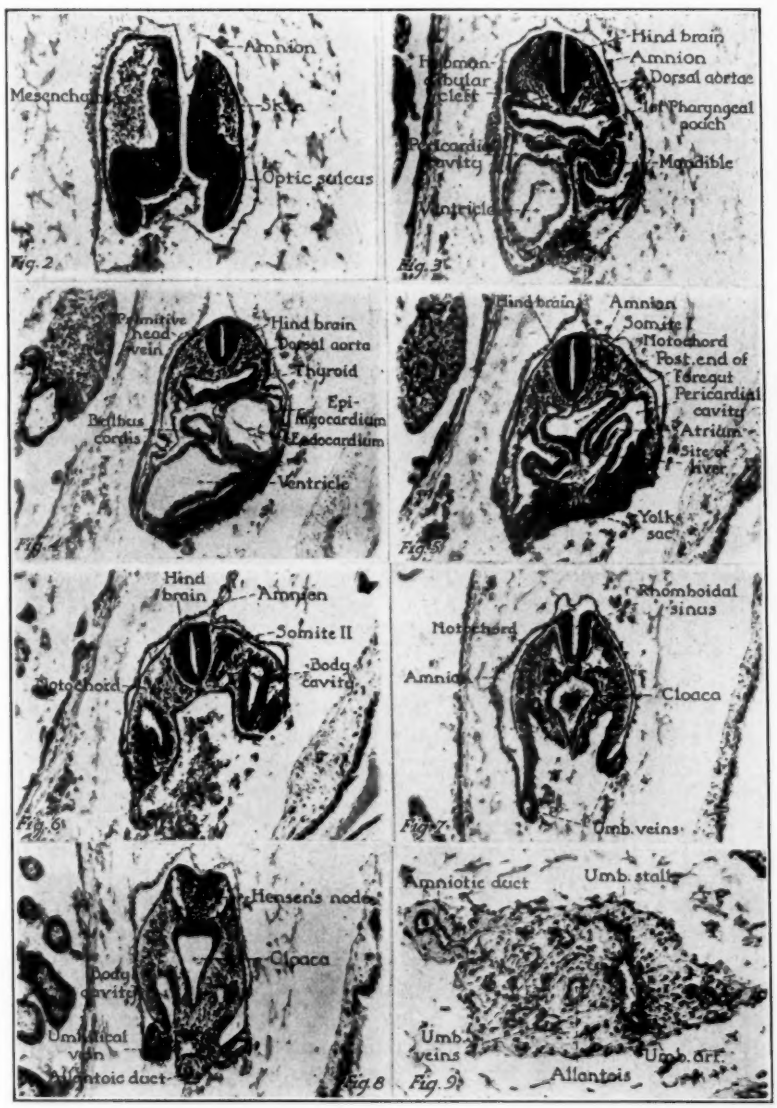
Fig. 1.—Showing the whole ovum within the decidua. Note the conelike form of the chorionic elements descending into the decidua basalis and the "tap root" villus burrowing clear through the compact decidua, deeply into the spongy, glandular area. Magnified 8 times.

formation comes from a determination of the stage of the embryologic development and the status of the specialization of the chorionic and decidual elements in their progress toward placentation.

It is the purpose of this study to determine these facts as nearly as possible. In the light of our present knowledge, even when the embryologic development has been accurately determined by microscopic study and reconstruction of the embryo, it is impossible to state the

age in days because, as yet, the rate of development is unknown and probably varies in each individual case.

The study of this ovum has been chiefly concerned with its placentation features, so only such embryologic data will be presented that may



Figs. 2 to 9.—Showing the stage of development of the embryo. These sections fix the approximate age of the embryo in the early part of the fourth week. Magnified 100 times.

help in determining its approximate age. Even if we are not trained embryologists, we obstetricians and gynecologists may be pardoned for occasionally using our material by dabbling in Embryology, for as Arey[1] says: "Obstetrics is to a large degree merely applied embryology."

The minute study of the embryo and its reconstruction will be undertaken by my colleague, a trained embryologist, Prof. Boyden, of the Department of Anatomy, of the University of Minnesota, to whom I am indebted for valuable help.

Judged by the table of characteristics of embryos during the various stages of development, our embryo fits quite accurately into the fourth week.

Arey[1] gives the following features, which first appear in the fourth week, most of which are demonstrable in our embryo and are indicated in the parenthesis in the quotation.

"There are high neural folds (Fig. 3) which unite into a neural tube (Fig. 4) whose expansive brain portion is plainly indicated (Fig. 2), the heart becomes conspicuous (Figs. 3, 4, and 5). There are paired blood vessels (see right and left aortas in Figs. 3, 4, and 5).

"The embryo is cylindrical (which is illustrated by all of the photomicrographs of this embryo) and two tubes, neural and enteric, with the notochord between (Figs. 5, 6, and 7); also the earliest branchial pouches (Fig. 3). The pharynx is broad and flat (Figs. 3, 4, and 5), the thyroid is a simple sac (Fig. 4), the notochord is a cellular rod (Figs. 6 and 7) and the optic and auditory placodes are indicated" (Figs. 2 and 3).

All these embryologic features, together with the number of somites (thirteen or fourteen), place the ovum quite definitely about the middle, or earlier in the fourth week of development.

THE EMBRYO

Length of the Embryo.—Fortunately, the embryo is cut in almost exact cross-sections, 8 microns thick, in 270 of which the embryo appears, which gives an approximate length of 2.16 mm. Because of immediate fixation, shrinkage would probably not be more than 10 per cent. This measurement also puts the ovum in the fourth week of development.

Formation of the Implantation Cavity.—A striking and unusual feature of this ovum is that the shape of the implantation cavity is cone-like. The tip of this cone is 8.1 mm. from the dome of the capsularis. A single long villus (there may be more than one) extends deeply into the decidua basalis, like the "tap root" of a plant, a distance of 2.4 mm. deeper than the tip of the cone, or 10.5 mm. from the capsularis dome. The cavity is 9.4 mm. wide, at its greatest width, and is 12.6 mm. thick at the same level (Fig. 1).

Streeter,[6] when describing the Miller ovum, noted that "at one place the trophoblast is seen to sink more deeply into the maternal tissues. The existence of this trophoblastic plug can only be accounted for by the view that the ovum has found its way into deeper tissues by active downward growth." Young also noted this phenomenon.

Size of the Chorionic Vesicle.—At its greatest size, the chorionic vesicle is irregularly oval and measures 4.3 mm., from top to bottom, 4.1 mm. from side to side, and is 8.7 mm. thick.

The size of the implantation and chorionic vesicle cavities are utterly unreliable in accurately determining the age of an ovum and even the length of the embryo is not conclusive.

"Size alone is too variable to be reliable. It is better to correlate the degree of development of the primitive mesodermal segments or somites" (Arey).

The number of somites (Figs. 5 and 6) in our ovum is thirteen or fourteen, which quite definitely puts it near the middle of the fourth week of development. The rate of growth and differentiation in man and the monkey run closely parallel in early development. The first somites make their appearance at the twenty-second day (Streeter).

By this analogy our ovum is more than twenty-two days old and probably not very much older, for Streeter adds that the somite development proceeds rapidly; one, five, and even eight somites are found on the same day, so their number is rather a question of hours instead of days. With the change from embryotrophic to the hemotrophic stage of nutrition the embryo begins to develop rapidly, because it has better nourishment by the maternal blood.

IMPLANTATION AND PLACENTATION OF THE HUMAN OVUM

The successive steps in early pregnancy are illustrated in the following pictures of the early ovum which forms the basis of the report.

Fertilization.—When ovulation projects the mature ovum into the abdominal cavity, it begins its "free life" of approximately ten days before implantation occurs.

The ovum, probably in a few hours, enters the distal end of the fallopian tube, where it is generally believed the union with the spermatozoan occurs, after which its development begins at once.

Migration of the ovum to the uterus probably takes three or four days (Teacher[5]). There is some difference of opinion as to the proportion of the ten or twelve days time between fertilization and implantation that is spent in the tube and in the uterine cavity, but the weight of opinion seems to favor the shorter journey through the tube, and the longer sojourn in the uterus.

The Sojourn in the Uterus.—The ovum does not pierce the uterine epithelium at once, but remains in the uterine cavity, nourished by the secretion from the uterine glands for some days, until the ectoderm has become capable of eroding the endometrium, which occurs about ten days after fertilization (Grosser,[4] Teacher,[5] Arey[1]). Glycogen and other nutritive elements are found in the premenstrual (pregravid) endometrial glands, undoubtedly in anticipation of nourishing the ovum during its stay in the uterine cavity.

Implantation.—When the extraembryonic ectoderm has developed all over the ovum, the time for implantation of the ovum has arrived, for it now has the erosive power. Arey says that "the entire process of implantation is completed in one day" and Teacher avers that "the ovum is quite within the endometrium in two or three hours." Although the process of human implantation has never been seen, by analogy with animals, we may safely infer that the ovum enters as a blastocyst, as von Spee demonstrated in the guinea pig, and Da Costa in the hedgehog, in both of which the blastocyst has a bipolar structure; the entering or implantation pole, at which the embryo and placenta (decidua basalis) will be formed, and the adhering or closing pole, which is the last to enter, leaving some of its cells in the aperture of entrance, which unite with those of the endometrium and probably fibrin, to form the operculum which closes the eroded opening, thus completing the permanent separation of the uterine from the implantation cavity.

Although the decidua capsularis of our specimen is, in places, very thin (Fig. 1) a careful search reveals no positive evidence of the operculum, which is quite in keeping with the findings of many investigators, who have found that all evidence of the operculum disappears rapidly.

Formation of the Primary Implantation Cavity.—Having penetrated the uterine epithelium the trophoblast at once begins en masse destruction of maternal tissue, to form the primary implantation cavity, at the same time opening small blood vessels, to furnish nourishment. This destruction, though general, is limited so that at this stage the decidua capsularis is rather close fitting, as seen in the Miller ovum, the youngest of all early ova, quite in contrast to our specimen, which shows no connection between the capsularis and the chorionic vesicle (Fig. 1).

The Primary Trophoblast.—At this time there are no villi, the whole ovum being surrounded by a mass of trophoblast, which consists of two types of cells, the cytotrophoblast, the analogue of the later Langhans' layer and the eroding plasmoditrophoblast, similar to the syncytium. This mass becomes vacuolated, which permits the released blood to enter it, much as a sponge absorbs water, thus furnishing the first blood supply to the ovum. This is the embryotrophic stage of nutrition, as distinguished from the hemotrophic stage, when the maternal blood really circulates in the intervillous space. The transition from the primitive to the permanent type of nutrition is gradual; both may be found in the same ovum (Grosser[4]). Most of the primary trophoblast degenerates, but remnants of it remain, at least during the earlier stages of development of the hemotrophic stage of placentation. In Fig. 19 such a degenerating mass of primary trophoblast is shown in our ovum, which is in the early hemotrophic stage.

The large venous sinus, which is so conspicuous in this fourth-week ovum (Figs. 1 and 13), is a prominent feature of nearly all young ova. Teacher[5] says that the connection with "the great venous sinus" is doubtless made during this earliest stage and survives during the succeeding phase of destructive activity. Just as the Miller ovum exemplifies the earlier stage of implantation, so the Teacher-Bryce I illustrates "the destructive stage in full activity" (Teacher). The primitive plasmodetrophoblast (syncytius) has excavated a relatively large implantation cavity, with necrotic walls and the cavity is filled with blood, which drains into the great venous sinus. "This marks the beginning of the circulation of blood around the ovum" (Teacher).

Separation of the Chorionic Vesicle from the Operculum.— By the end of the destructive stage the chorionic vesicle separates from the decidua capsularis, to which it was earlier attached, at the operculum, which soon disappears, as illustrated in this ovum (Fig. 1).

Development of the Permanent Trophoblast.—The entire picture of the development of the implanted ovum depends upon the progress of the trophoblast, step by step, from the primary mass of trophoblast to the mature placenta (Grosser[4]). The next step is the change from primary to the permanent trophoblast, which destroys the first plasmodetrophoblast and replaces the primitive cytoblast, from which in turn the permanent syncytium develops. Mass destruction, as seen in the Teacher-Bryce I ovum, is succeeded by a methodical attachment of the ovum to the decidua by the villi (Fig. 13), which also deliberately open the blood vessels (Figs. 11 and 12) and establish an orderly circulation in the intervillous space, which is maintained up to the full maturity of the placenta.

Placentation.—Strictly speaking, placentation begins immediately after penetration of the epithelium. All the preliminary steps mentioned, are phases leading up to the formation of the permanent villi in the chorion frondosum and the development of the decidua basalis, which together eventually form the mature placenta. All the elements necessary to this end are now present, so we have the beginning

of the final hemotrophic phase of placentation, which has for its objective the nourishment of the embryo and fetus by the mother's blood, through the villi, and by way of the fetal circulation, which is now not far distant.

The Decidua, Compact Layer.—In truth the preliminary steps toward placentation occur during ever menstrual cycle, when the endometrium is prepared for nidation of the ovum. The decidua is really on its way during the premenstrual (pregravid) stage of the cycle, as is shown by the increased blood supply, the secreting glands, containing food elements and the swelling of the connective tissue cells, which are

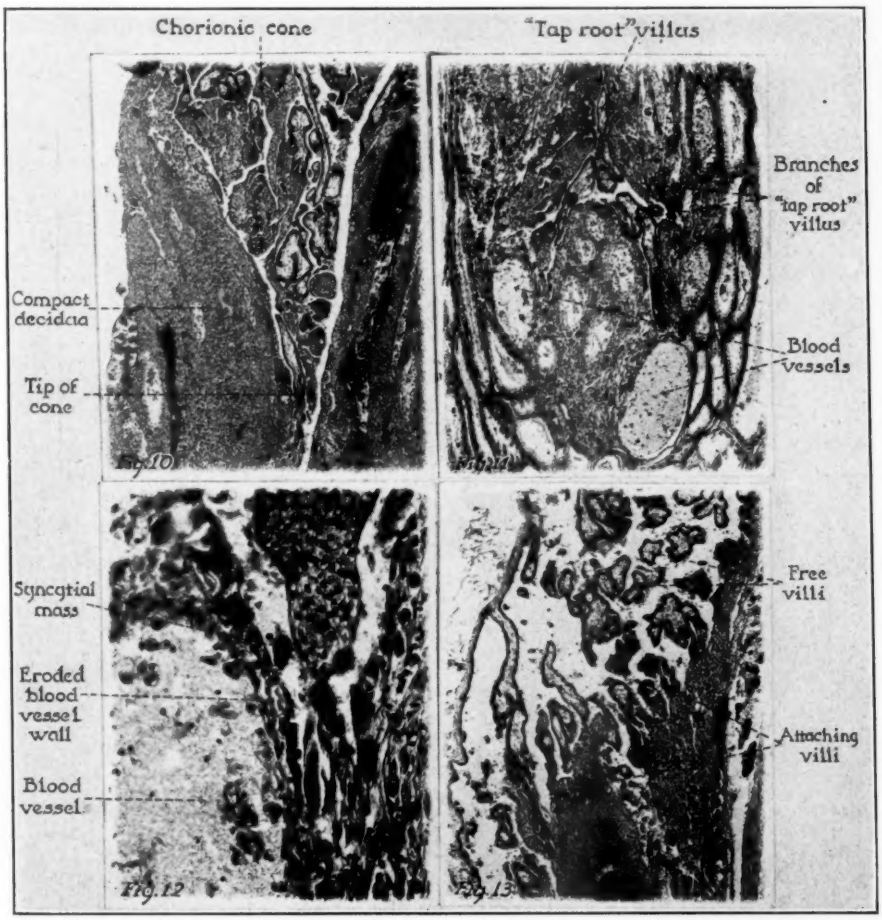


Fig. 10.—Shows the conelike descent of the chorionic elements into the compact decidua. Magnified 60 times.

Fig. 11.—Shows the "tap root" villus having pierced the compact decidua into the spongy layer and has divided like a "Y," each branch attacking a different vessel. Magnified 60 times.

Fig. 12.—Shows the detail of the villus attacking the vessel on the left, in Fig. 11. Magnified 400 times.

Fig. 13.—Shows "fastening villi" attaching themselves to the compact decidua. Magnified 200 times.

the forerunners of, and have not infrequently been mistaken for decidual cells. These cells, after fertilization, even before implantation begin to enlarge, probably by endocrine influence and continue their development well into the hemotrophic stage of nutrition.

The decidual cells differ greatly in the various reported young ova; some of the youngest ones show very little decidual formation and that only in the vicinity of the ovum, probably because they are not required for nourishment until later (Teacher,[5] Grosser[4]). The compact layer is well illustrated in Figs. 1, 10, and 14.

In this ovum the decidual cells are highly developed and illustrated in Fig. 14, as large cells, packed together, showing the familiar mosaic pattern. The cytoplasm is clear, with a round or oval, darkly stained or granular nuclei. These cells were photographed in a field, a little distance from the ovum. The cells in Fig. 15

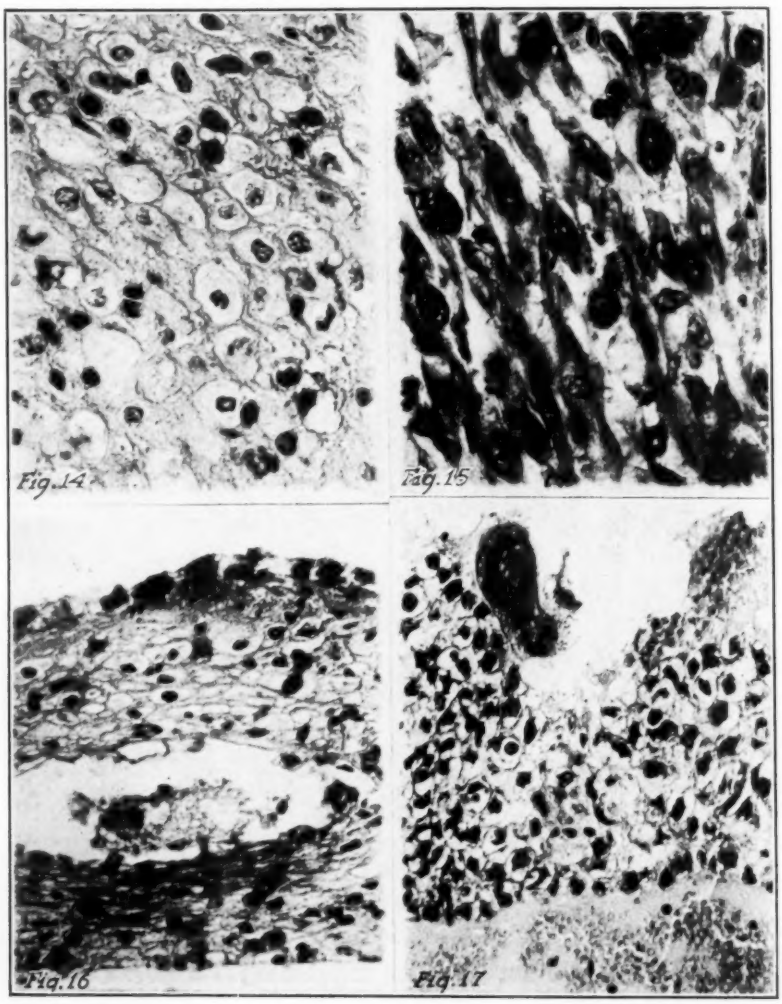


Fig. 14.—Shows the typical mosaic of well-developed compact decidual cells. Photographed some distance from the ovum. Magnified 550 times.

Fig. 15.—Also shows decidual cells in the immediate vicinity of the ovum. Note the more connective tissue type of cell, the lesser swelling and darker staining, and their separation by edema.

Fig. 16.—Shows the cells in the decidua capsularis with a blood vessel in the center. Note the much less developed decidual cells.

Fig. 17.—Shows a mass of primary trophoblast surrounded with blood. Note vacuolization permitting blood to soak up for the primitive "Embryotrophic" nutrition. At upper left is shown degenerating mass, which will be the ultimate fate of the entire mass. All are magnified 550 times.

taken in a field, near the ovum, show a somewhat different picture. They are more elongated and are not packed so closely, being separated, apparently, by edema.

Decidua Capsularis.—In the decidua capsularis (Fig. 16) the decidual cells are much less developed, or regressing. They are not so large, are more oval, and more nearly like the connective tissue cells of premenstrual endometrium, but they have the same clear cytoplasm, usually with oval nuclei. Pigment, vacuoles, and leucocytes are scattered throughout the capsularis and show signs of their inevitable destiny, degeneration. No glands are found in the capsularis, as might be expected, as it is made up of compact decidua. There is only, occasionally, degenerated epithelium anywhere over the capsularis. Blood vessels are scarce, although one is shown in Fig. 16.

Decidua Basalis.—The decidua basalis, the future site of the placenta, is composed of both compact and spongy layers. The compact layer is easily eroded by the villi and offers opportunity for fastening the ovum to the uterus by the attachment villi (Fig. 13). The glands of the spongy layer resist attack by the villi.

Spongy Layer of the Basalis.—A prominent feature of this ovum is the enormous size of the long, perpendicular glands, with the characteristic appearance of the "saw tooth pregnancy gland" of Opitz. They are still active, although evidently on the way toward regression. The great development of the glands, in all probability, is for the purpose of furnishing nourishment, "the uterine milk" of the older authors, and called "embryotrope" by the Germans. In the secretion, glycogen, albuminoids, and possibly lipoids are found (Lenzenmeier[9]). One of the "saw tooth" glands is shown in Fig. 18, illustrating all phases of secretion, normal, high columnar cells, with nuclei at the base, others about to discharge their secretion, some just doing so, while others have already thrown out the secretion and show signs of degeneration. In the lumen is blood, a common finding in pregnancy; coagulated secretion and cellular débris.

The Villi.—As mentioned before, one of the conspicuous features of this ovum is the conelike descent of the chorionic elements, the villi with their syncytial masses at their tips, deeply into the decidua basalis (Fig. 10).

The "tap root" villus (or villi) may be seen in Figs. 1 and 11, having passed through the compact layer to the spongy layer, where it divides like a Y, each branch going to attack a separate vessel, a graphic illustration of the, almost uncanny, biologic design behind the process of placentation.

In Fig. 12, under higher magnification, the syncytium is shown having almost completely destroyed the wall of the vessel from which blood is escaping. Thus the orderly establishment of the maternal circulation in the intervillous space proceeds.

Villi are very numerous and long in the basalis, some of them attaching themselves to the decidua, but most of them floating freely in the maternal blood. Villi, on the side of the chorionic vesicle (Fig. 1) toward the basalis, are fewer and are destined to eventual complete degeneration.

The agency by which the vessels are opened is the syncytium, seen distinctly as a heaped up mass of cells, at the tip of the villi, attacking the vessels in Figs. 11 and 12. The two layers of trophoblast, covering the villi, are well shown in Figs. 19 and 21. The inner Langhans' layer consists of cells, with a distinct cell wall and moderately clear cytoplasm, with sometimes pale and sometimes darker nuclei, running parallel to the surface of the villus. In the outer syncytial layer no cell membrane is seen.

The cytoplasm is of plasmodia nature and is pale and vacuolated. The nuclei are oval and dark staining (Fig. 21). These layers are highly specialized, which marks this ovum as belonging to the beginning hemotrophic period of nutrition of the embryo.

Angiogenesis and Hemogenesis.—While the procedure of eroding vessels is progressing toward establishment of the maternal circulation around the villi, a very interesting process is going on within the villi and chorionic vesicle wall, having for its objective, establishment of the fetal villous circulation, the formation of fetal vessels in situ, within the walls of the villi.

Streeter[7] observed its earlier manifestation in his report of the Mateer ovum, which belongs to the presomite stage of development of the embryo.

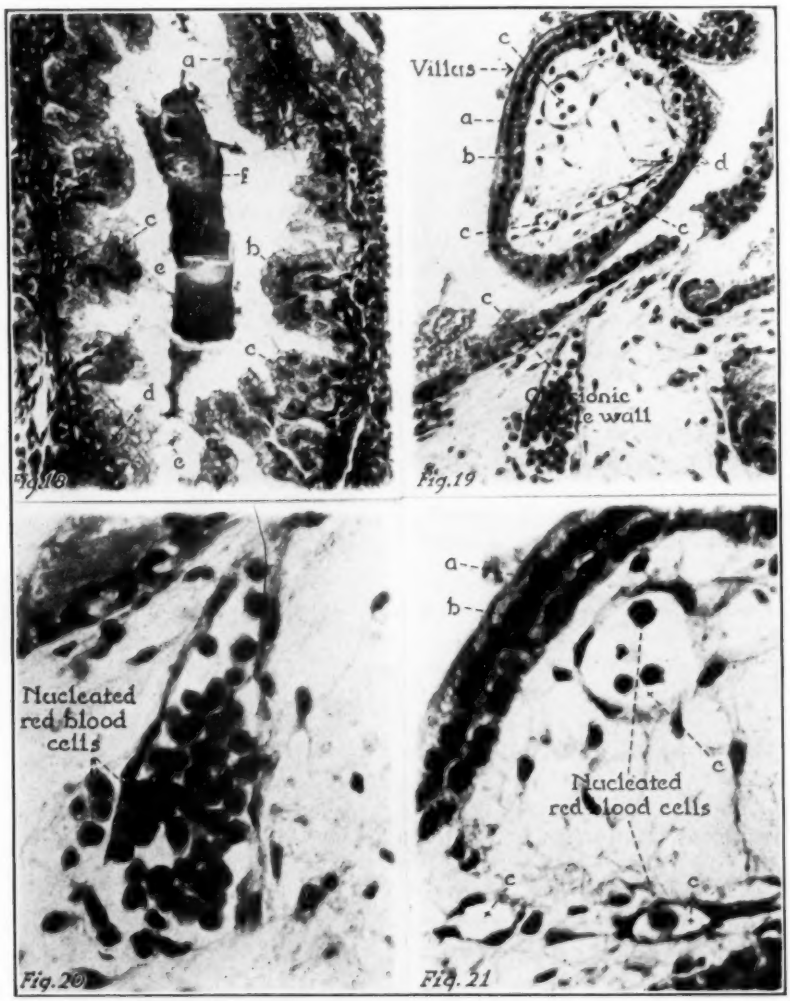


Fig. 18.—Shows the enormously enlarged "pregnancy gland" of Opitz. *a*, Non-secreting gland epithelium. *b*, Cells about to discharge secretion. Note vacuoles of secretion at tip of cells. *c*, Secretion being discharged. *d*, Secretion discharged. *e*, Coagulated discharge in lumen of gland. *f*, Coagulated blood in lumen of gland, a common finding in the pregnancy glands. Magnified 100 times.

Fig. 19.—Chorionic vesicle wall and villus showing developing blood vessels and red blood cells in situ and also the two trophoblastic layers. *a*, Syncytial layer without cell membrane. *b*, Langhans' layer with definite cell membrane. *c*, Developing blood vessel, angiogenesis. *d*, Strands with nuclei from which blood vessels and their endothelium develops. Magnified 100 times.

Fig. 20.—Showing detail of the developing blood vessel in the chorionic vessel wall of Fig. 19. Note nuclei in vessel wall which will become the endothelium of the vessel; also the nucleated red cells within and without the vessel. Magnified 800 times.

Fig. 21.—Detail of villus in Fig. 19. *a*, Syncytium. *b*, Langhans' layer. *c*, Vessel showing developing endothelium.

In the meshes of the stroma, condensed angioblastic strands are seen, along which are scattered nuclei (Figs. 19 and 21). These strands gradually form tubes with nuclei in their walls, which will become the endothelium of the mature vessels. Streeter saw cells suspended between the two walls by slender threads, future blood cells. In our specimen we find the process a little more advanced with numerous nucleated red blood cells within and without the primitive vessels. The various stages of this process of angiogenesis are illustrated in Figs. 19 and 21, where it may be seen in both the chorionic wall and a villus.

Under high magnification the partially formed blood vessel in the wall of the chorionic vesicle is seen filled with nucleated red blood cells. Some of the cells are outside the vessel. The developing endothelium is also distinctly seen (Figs. 20 and 21). The different steps of angiogenesis are nearly all observed in the villus; the strands with nuclei, partially formed tubes, with nucleated red cells within, and endothelial formation.

SUMMARY

A young human ovum is presented, with an embryo of the early somite period. The specimen was found in a uterus removed for multiple myomas.

It shows nearly all of the characteristics of an embryo, in the fourth week of development.

The chorionic elements show the earmarks of the early hemotrophic stage of activity and differentiation; attachment villi, erosion of vessels, angiogenesis, and hemogenesis. Placentation is in a very early stage, but is very definite. Peculiar features of this ovum are the cone-like descent into the decidua basalis with a "tap root" villus eroding its way deeply into the spongy decidua and dividing to erode vessels, thereby establishing the maternal circulation in the intervillous space.

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1009 NICOLLET AVENUE

AN ANALYSIS OF A SERIES OF NONCONVULSIVE CASES OF TOXEMIAS OF PREGNANCY*†

FRED L. ADAIR, M.D., CHICAGO, ILLINOIS

(From the Department of Obstetrics and Gynecology, The University of Chicago, and The Chicago Lying-In Hospital)

THE toxemias of pregnancy constitute one of the most important and interesting problems in the field of obstetrics—important because they contribute so much directly and indirectly to fetal and maternal morbidity and mortality, and interesting because we know so little about them from an etiologic point of view. We have much empiric knowledge, both from a clinical and laboratory standpoint, but we know relatively little about the causation and ultimate effect of this varied group of conditions known as the toxemias of pregnancy. Not all of these conditions are, fundamentally, toxemias of pregnancy. Some of them are certainly manifestations of underlying conditions which are brought out by the additional strain of pregnancy.

The division of these conditions into nonconvulsive and convulsive types of toxemia is not scientifically sound, nor is there any etiologic reason for such a classification. It does, however, give a rather sharp clinical and symptomatic grouping. It is also a criterion of the efficacy of prenatal care and is a measure of the completeness with which such care is administered to the individual patient in practice or in any clinic. The more general and complete the prenatal care, the fewer the number of convulsive cases. It was thought that eclampsia could be prevented by prenatal care. We now believe that we do not decrease the number of potential eclamptics of the convulsive type, but that we detect the premonitory symptoms and institute treatment of varying kinds and forestall, as a rule, the onset of the convulsions. This increases the number of preeclamptics and the nonconvulsive group, and diminishes the number of eclamptics and the convulsive group.

For twenty years we have had active propaganda for adequate maternal care. Prenatal care is an essential part of this health activity, especially for the control of toxemias of pregnancy. A study of maternal mortality carried out by the Children's Bureau, and about to be published, has analyzed the causes of 7,380 maternal deaths. In 6,226 the pregnancy ended after the third month of gestation. Some prenatal care might have been expected in this group. A report, rela-

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tive to such care, was obtained in 5,636 cases. Of these, 3,025, or 54 per cent, received no prenatal examination by a physician. The remaining 2,611 received some care by a physician, which may be graded as follows, according to "Standards of Prenatal Care" (Children's Bureau Publication No. 153):

Grade I (a)	42 women, or less than 1 per cent
Grade I (b)	683 women, or 12 per cent
Grade II	499 women, or 9 per cent
Grade III	1,337 women, or 24 per cent

About 50 other women had some prenatal care but were not classified. If one considers the 4,570 who reached the last trimester, as a separate group, prenatal care of Grade I was given to 12 per cent, of Grade II to 10 per cent, and of Grade III to 26 per cent, and no care to 51 per cent.

The care received by the toxic group was no more satisfactory than for the entire series of fatal cases. About one-half, 49 per cent of 1,756 studied cases, had received some prenatal care, which may be graded as follows:

Grade I	218 women, or 12 per cent
Grade II	159 women, or 9 per cent
Grade III	463 women, or 26 per cent
Ungraded	14 women, or 1 per cent
No care	902 women, or 51 per cent

About one-third of these women were dead, comatose, or in convulsions when first seen by a physician. Only about one-fifth were in good and less than two-fifths were in fair or good condition when medical aid was first available.

In view of these facts it is not surprising that in the total of 7,380 fatal cases, there were 2,221, or 30 per cent, which were preceded by some probable toxemia. Most of these, 1,900, or 26 per cent of the total, were due to the so-called puerperal albuminuria and convulsions (No. 148). As a cause of maternal mortality this one is exceeded only by puerperal septicemia. However, if one considers only the last trimester of pregnancy, when the toxemias are most frequent, the mortality from sepsis and that from toxemia are equal, namely, 31 per cent. In rural communities it exceeds sepsis as a cause of maternal deaths at this period of gestation. In addition to this group of fatalities, there is a smaller group (3 per cent) in which toxemias were the chief contributory cause. Most of these patients died from sepsis as the primary cause.

The fetal deaths in these toxic cases were enormous. Many mothers died undelivered and, in addition, there were 457 stillbirths and 807 living births. The number of neonatal deaths was not determined in

this study. In the total of 1,900 women, 23 per cent were undelivered at the time of death. Even of those dying in the last trimester, 1,549 of the 1,900 cases, one-fifth died undelivered. Of those remaining, the terminations were evenly divided between spontaneous and artificial. The women dying in the first two trimesters were undelivered in about one-half of the instances, and approximately one-quarter had spontaneous and artificial terminations. Over 68 per cent of the fatalities from toxemia had convulsions, so that the minority of deaths was in the nonconvulsive type. The number of patients, stated to have had convulsions, was 1,305, no convulsions, 521, and not determined, 74.

Of the convulsive patients who were delivered before death, 56 per cent died within the first twenty-four hours, and 90 per cent within the first week. On the other hand, 31 per cent of the nonconvulsive patients died within the first day, and 63 per cent within the first week. About 2 per cent of the former and 14 per cent of the latter lived four or more weeks.

Parity and age seem to be related to the mortality. Puerperal albuminuria and convulsions caused the deaths of 36 per cent of the primiparas, from 21 to 24 per cent of para ii to para vii, 18 per cent of deaths of para viii to para ix, and 24 per cent of those of para x and subsequent parities. It seems to be more serious in younger primiparas, as it caused 41 per cent of the deaths of primiparas under twenty years, 37 per cent of the deaths of primiparas between twenty and twenty-five years, and 29 per cent after twenty-five years. In multiparas there is little variation in different earlier age groups, as it occurs in from 19 to 20 per cent of these groups. There is an increase to 23 per cent in the age group of thirty-five to thirty-nine years, and to 28 per cent between forty and forty-four years.

The history of previous kidney disease was not at all complete, but in 729 of these cases in which some past history was obtainable, past kidney disease was mentioned in 33 per cent, while in 2,105 women who died from causes other than toxemia, kidney disease was referred to in only 8 per cent of the cases.

The result of treatment was tragic in all of these cases, but of 1,723 patients, 32 per cent were convulsive or comatose, 29 per cent were in otherwise poor condition, 18 were classed as fair and 21 per cent as in good condition when first seen by the physician. Of 1,029 (54 per cent) women who were hospitalized, 866 were in serious condition at the time of admission. The onset of labor was artificial in 32 per cent, spontaneous in 21 per cent, and death occurred without labor in 47 per cent of the cases which were fatal in the first two trimesters. Of those dying in the last trimester, 14 per cent had no onset of labor, 26 per cent had an artificial onset, usually mechanical, including many cases of accouchement forcé, plus 146 cesarean sections.

In the whole series of 7,380 cases, there were 537 cesarean sections, and in these the principal indication reported was eclampsia 165, pre-eclampsia 47, and uremia 27, making a total of 239 cases. Local anesthesia was used in 19, chloroform in 14, and ether in 150 of these cases. In all of the cases, operative delivery was done in 42 per cent, spontaneous termination occurred in 41 per cent, and no delivery in 18 per cent. The surgical procedures in the 702 cases having operations were: cesarean sections 29 per cent, version 7 per cent, cervical dilatation and version 16 per cent, forceps 22 per cent, cervical dilatation plus forceps 14 per cent, cervical dilatation 9 per cent, and other operations 3 per cent. There were very few autopsies in the whole series, so little information of value is available, relative to the underlying pathology.

Our series of cases has been accumulated from the records of the new Chicago Lying-in Hospital and cover a period of time of, approximately, one and one-half years. This represents observations on about 262 pregnancies with signs of nonconvulsive toxemia in which series 255 represent single pregnancies, 6 two pregnancies, and 1 three pregnancies. (The series is not consecutive, nor are the data complete from either a clinical or laboratory point of view. These cases have been considered and included in the series as they presented themselves to the clinic, and do not constitute a group of cases upon which intensive study has been made. All fatalities of mother and fetus have been included.)

We have not attempted to compare this group with a very small number of convulsive cases, which have been admitted to the hospital during this period of time. The number of cases having convulsions has been minimal, and is, approximately, 17.

The average age of patients in our series of nonconvulsive toxemia was twenty-nine, the youngest being seventeen and the oldest forty-six. (The average age of women pregnant for the first time was twenty-five, the youngest being seventeen and the oldest forty-one. The average age of those going to term, with previous abortion, was thirty, the youngest being eighteen and the oldest forty-six. The average age of the para ii was thirty, the youngest being eighteen and the oldest forty-two. The average age of those having had three or more pregnancies was thirty-five, the youngest being twenty-three and the oldest forty-five.)

(The height of the patient is not material in this connection, but the average height of 152 individuals was 155 cm., the shortest being 109 and the tallest 173.)

The average weight of 214 patients, based on the initial weight when first seen in the clinic, was 68.8 kg., the minimum weight being 43.3 kg., and the maximum 125 kg.

The average number of pregnancies for a series of 262 cases was 3.06, the minimum 1, and the maximum 18. (The number of parities in 262 cases, including existing pregnancy, was 2.49, with a minimum of 0, and a maximum of 15.) The average period at which gestation was terminated in 246 cases was thirty-seven weeks, the minimum number of weeks being eleven, and the maximum menstrual age forty-four weeks.

One has to consider the weight increase during the period of observation. (The figures for this are relative, but give some idea of weight alterations. A few patients lost weight during the antepartum period. The figures are calculated for the period of weeks during which the patient was under observation, beginning with the initial weight and using the maximum recorded weight prior to delivery.) This shows an average kilogram increase of 8.49 for an average period of thirteen weeks, which represents an average increase per week of 0.65 kg. The maximum weight loss was 1 kg. in five days, and the maximum weight gain was 25.5 kg. in twelve weeks.

In considering the weight increase, the arbitrary figure of 0.5 kilogram per week was taken as a standard, and the weight gain considered for a series of 104 cases showing a weight increase in excess of this amount. They averaged 11 kg. for an average period of fourteen weeks; the maximum was 25.5 kg. in twelve weeks; and the minimum was, naturally, 1½ kg. in three weeks.

For the series of 42 cases, showing a weight increase averaging less than 0.5 kg. per week, the average weight gain was 4 kg. in fourteen weeks; the minimum was, naturally, ½ kg. in one week, with a maximum of 3 kg. in seven weeks.

There were 7 cases in this series which showed an average antepartum decrease of 2 kg. in seven weeks; the minimum being 1½ kg. in fifteen weeks, and the maximum, 1 kg. in five days.

One could consider a weight increase of one-half kilogram, or more, per week as being abnormal. On this basis, 104 of 262 pregnancies in this series showed abnormal weight increase. This is a percentage of 40. One would be justified in concluding that determination of weight is an important clinical observation and that about 40 per cent of nonconvulsive cases show an abnormal increase in weight during pregnancy.

We have also a considerable number of routine blood pressure observations. (It was impossible, of course, to have blood pressure readings on patients prior to their initial visit when our prenatal observations began. Unfortunately, our prenatal care falls short of being ideal. Only 41 of 240 cases appeared in the first four lunar months, 81 appeared for the first time between the sixteenth and twenty-fourth weeks, 73 between the twenty-fourth and thirty-second week, and 45

made their appearance in the clinic after the thirty-second week.) Our prenatal care may be said, therefore, to have begun in the first four lunar months in 17 per cent of our cases, in the fifth and sixth lunar months in 34 per cent, in the seventh and eighth lunar months in 30 per cent, and in the last two lunar months in 19 per cent. A certain percentage of the cases first came under observation when admitted to the hospital in labor, so that our own series of initial prenatal blood pressure readings is incomplete.

It is interesting to note that in 130 of the 240 cases, or 54 per cent, the initial blood pressures were under 130 systolic; 82, or 34 per cent, ranged from 130 to 170, and only 28, or 12 per cent, ranged from 170 to 200 or more.

Sixteen of 21 initial blood pressure readings in excess of 170 occurred in the last trimester of pregnancy. Only one initial blood pressure reading over this height was obtained in the first trimester. These readings averaged 130 systolic and 78 diastolic, with a minimum of 90 systolic and 30 diastolic, and a maximum of 250 systolic and 140 diastolic. (Table I.)

TABLE I. INITIAL SYSTOLIC BLOOD PRESSURE BY WEEK OF GESTATION

	90	100	110	120	130	140	150	160	170	180	190	200			
12	0	2	4	7	1	2	0	2	1	0	0	0	19	}	41
16	2	2	3	10	2	2	0	0	0	0	0	1	22	}	
20	1	2	12	10	5	2	2	0	2	0	0	1	37	}	81
24	2	6	6	5	8	6	2	3	1	1	1	3	44	}	
28	0	3	9	8	2	3	3	4	0	0	1	0	33	}	73
32	3	2	4	10	5	5	5	1	4	1	0	0	40	}	
36	0	2	6	7	3	4	3	0	1	1	2	2	31	}	45
40	0	0	0	2	3	2	1	1	3	0	0	2	14	}	
	8	19	44	59	29	26	16	11	12	3	4	9	240		
		130				82				28					

The blood pressure was also studied from the time of appearance of first recorded increase. This initial antepartum rise was recorded in 216 cases, ranging up to 130 in 27, or 13 per cent, of the cases; from 130 to 170 in 145 cases, or 67 per cent, and 170 or above in 44 cases, or 20 per cent. It is interesting to note that this initial rise of blood pressure was observed in the first four lunar months in only 6, or 3 per cent, of the cases; in 14, or 6 per cent, in the fifth and sixth lunar months; 38, or 18 per cent, in the seventh and eighth lunar months, the vast majority occurring in the ninth and tenth lunar months and mounting to 157, or 73 per cent, of the cases. No doubt more frequent blood pressure observations would have altered this time incidence considerably. The initial increase was manifested and an average rise

to 152 systolic, and 91 diastolic, noted; the minimum initial rise being up to 105 systolic and 50 diastolic; the maximum to 270 systolic and 158 diastolic. (Table II.)

The initial rise in cases with hypotension may be manifested by a reading which is well within, or even below, the average normal blood pressure and indicates the importance of securing blood pressure observations early in pregnancy. An increase of blood pressure in a case with hypotension may be of equal significance to a rise above normal in a case where the usual blood pressure is normal, or slightly in excess of the normal average; that is to say, the blood pressures and the actual readings are, in a measure, relative and not absolute.

Figures were also compiled relative to the maximum antepartum reading. The average maximum antepartum reading attained in these nonconvulsive cases was 171 systolic, 105 diastolic; the minimum 120

TABLE II. INITIAL RISE IN BLOOD PRESSURE BY WEEK OF GESTATION

	110	120	130	140	150	160	170	180	190	200		
12	0	0	1	0	1	0	0	0	0	0	2	6
16	0	1	0	0	1	0	0	0	1	1	4	
20	0	0	0	2	1	1	0	0	0	0	4	14
24	0	1	1	4	1	0	1	0	0	2	10	
28	0	1	2	3	1	2	3	1	0	1	14	38
32	1	3	6	1	2	3	2	1	4	2	25	
36	1	6	17	17	12	10	9	1	0	1	74	157
40	2	11	18	16	11	11	4	5	3	2	83	
	4	23	45	43	30	27	19	8	8	9	216	
	27		145				44					

systolic, 61 diastolic; the maximum 258 systolic, 160 diastolic. This maximum, prior to actual delivery, was less than 130 in 9 cases, or 4 per cent; there were 113 cases, or 45 per cent, which ranged from 130 to 170; 128, or 51 per cent, in excess of 170. It is noteworthy that this maximum rise in blood pressure was attained in only 6 cases, or 2 per cent, in the first four lunar months.

Of these 6 cases, 3 were terminated by hysterectomy in the first trimester, two because of hypertension and one because of a nephritis without marked hypertension; one was terminated at the twentieth week by hysterotomy on account of marked hypertension and two went to term without aggravation of symptoms.

The patient with nephritis returned approximately two months later with no hypertension, clear urine, and disappearance of edema. This patient had also had a complicating ovarian cyst at the time of hysterectomy. The two remaining patients whose pregnancies were terminated by hysterectomy returned to the clinic for further observation. One patient was followed for four months, carrying a marked hyper-

tension of 184/134, with a faint trace of albumin in urine. The other patient has been followed for, approximately, eight months and carries a blood pressure of 190/106, which is an increase above the initial reading during pregnancy. This patient has not been cooperative and has had subjective symptoms of failing vision and severe headaches.

The patient whose pregnancy was terminated by hysterotomy did not return to the clinic for a postnatal visit. Of the two patients who went to term, one was subsequently followed for five months, at the end of which time her blood pressure reached normal and the urine became clear; the other patient was followed about one month when her blood pressure returned to normal.

The maximum blood pressures, prior to actual delivery, occurred in the fifth and sixth lunar months in 12 cases, or 5 per cent; in the seventh and eighth lunar months in 20 cases, or 8 per cent. The vast

TABLE III. MAXIMUM RISE IN BLOOD PRESSURE BY WEEK OF GESTATION

	120	130	140	150	160	170	180	190	200		
12	1	0	1	1	0	1	0	0	0	4	6
16	0	0	0	0	0	0	0	1	1	2	
20	0	0	0	0	0	0	0	0	0	0	12
24	1	1	1	0	1	2	0	1	5	12	
28	0	1	1	0	2	1	1	0	1	7	20
32	2	1	0	1	0	0	2	3	4	13	
36	1	2	1	9	7	14	4	6	13	57	212
40	4	8	13	36	26	24	15	13	16	155	
	9	13	17	47	36	42	22	24	40	250	
	9	113				128					

majority occurred in the ninth and tenth lunar months, 212 cases, or 85 per cent. Of this number 155, or 62 per cent, occurred in the last lunar month. (Table III.)

In the puerperium, the average maximum recorded blood pressure reading was 160/99, with a minimum of 110/65 and a maximum of 244/165. These maximum elevations are indicated according to the day of the puerperium. The maximum height after delivery was less than 130 in 17 cases, or 7 per cent, of 229 cases, ranged between 130 and 170 in 144 cases, or 63 per cent, and over 170 in 68 cases, or 30 per cent.

The maximum blood pressure reading in the puerperium was on the first or second day in 98 cases, or 43 per cent; on the third and fourth days in 50 cases, or 22 per cent; on the fifth and sixth days in 33 cases, or 14 per cent; on the seventh and eighth days in 27 cases, or 12 per cent; on the ninth, tenth and consecutive days in 21 cases, or 9 per cent. This indicates a definite recession of the blood pressure during the puerperium.

The blood pressure on discharge averaged 137/89, with a minimum of 100/48 and a maximum of 258/160. Of the blood pressure readings obtained, there were 52 cases, or 20 per cent, who had, prior to or at the time of discharge from the hospital, blood pressure readings on a level with their initial reading. Ninety-five cases, or 42 per cent, had a blood pressure reading on discharge above the initial reading. Seventy-six cases, or 34 per cent, had a blood pressure reading on discharge less than that of the initial reading.

The blood pressure readings on discharge, about the tenth day or later, were less than 130 in 34 per cent of the cases, ranged from 30 to 170 in 58 per cent, and from 170 to 200 in 8 per cent. (Table IV.)

TABLE IV. MAXIMUM BLOOD PRESSURE RISE DURING PUERPERIUM

	110	120	130	140	150	160	170	180	190	200			
1	2	3	1	16	13	10	7	5	7	7	71	98	
2	1	1	4	3	7	4	2	2	0	3	27		
3	0	2	7	7	9	1	1	1	1	2	31	50	
4	0	1	2	1	4	2	2	4	1	2	19		
5	0	1	3	3	3	5	1	2	0	1	19	33	
6	1	1	1	3	3	1	0	2	1	1	14		
7	0	2	2	2	3	3	0	2	1	1	16	27	
8	0	1	3	2	0	2	0	1	1	1	11		
9	0	0	1	0	1	0	1	0	0	0	3	21	
10	0	1	3	4	4	1	1	0	0	4	18		
	4	13	27	41	47	29	15	19	12	22	229		
	17		144				68						

Unfortunately, only 62 patients returned for postnatal observation, and of these 24, or 39 per cent, had a blood pressure less than 130. Twenty-six cases, or 42 per cent, ranged from 130 to 170, and 12 cases, or 19 per cent, ranged from 170 to 200, or more. This percentage figure is not a fair index, as the postnatal follow-up was very incomplete.

The average blood pressure of those patients who returned for postnatal observation was 138/89, with a minimum of 102/59 and a maximum of 220/134. (Table V.)

These postnatal readings were made at periods from one-half to fifteen months subsequent to discharge from the hospital. The urinary findings in these cases showed a trace of albumin in the urine in two cases and a heavy trace in one.

Recorded observations relative to edema were found in 66 per cent of the cases. The month at which the inception of this finding was noted was 2 per cent in the fourth month, 3 per cent in the fifth month, 6 per cent in the sixth month, 10 per cent in the seventh month, 9 per cent in the eighth month, 22 per cent in the ninth month, and 14 per cent in the tenth month.

Of these cases, 85.76 per cent showed albumin some time or other in their pregnancy. This first appeared in the first lunar month in 0.38 per cent of the cases, in 0.38 per cent in the second month, in 2 per cent in the third month, in 3 per cent in the fourth month, in 3 per cent in the fifth month, in 6 per cent in the sixth month, in 8 per cent in the seventh month, in 12 per cent in the eighth month, in 25 per cent in the ninth month and in 26 per cent in the tenth month.

Casts were found in only 1.92 per cent of the cases; 0.77 per cent in the seventh month, 0.38 per cent in the ninth month, and 0.77 per cent in the tenth month. The occurrence of white blood cells was not tabulated, but pus was stated to be present in 1.15 per cent of the cases; 0.77 per cent in the ninth month and 0.38 per cent in the tenth month. This finding was not based upon catheterized specimens.

We have records of 46 eyeground examinations on these patients, of which 30 were normal and 16 abnormal. Three of these abnormal

TABLE V. POSTNATAL BLOOD PRESSURE READINGS

	100	110	120	130	140	150	160	170	180	190	200	
MONTH	1	1	11	5	3	1	3	0	1	0	0	25
1	0	0	1	4	3	1	0	1	1		2	13
2	0	0	0	2	0	0	0	0	1	0	1	4
3	0	1	3	1	1	0	0	0	0	0	0	6
4	1	1	2	1	1	0	0	1	0	0	0	7
5	0	1	1	0	0	0	0	0	1	1	2	6
6	2	4	18	13	8	2	3	2	4	1	5	61
		24			26				12			

cases showed arteriosclerosis, one retinal, and one with hemorrhage. There were 9 cases showing retinitis, 5 hypertensive, 2 albuminuric and 2 neural. There was one case each showing hazy eyegrounds, edema, disseminated choroiditis, and hemorrhage.

The different symptoms complained of were as follows: headache in 118 cases, visual disturbances in 52 cases, dizziness in 39 cases, epigastric pain in 42 cases, constipation in 55 cases, and nausea and vomiting was a definite symptom in 43 cases in the first trimester, 23 cases in the second trimester, and 23 cases in the third trimester.

We have notations relative to previous illnesses in a considerable number of cases. Scarlet fever occurred alone or in combination with other diseases, excluding diphtheria, in 29 cases. Diphtheria occurred alone or in combination with other diseases, excluding scarlet fever, in 17 cases. Scarlet fever and diphtheria occurred in combination with other diseases in 11 cases.

Pneumonia was recorded in three instances. There was one case with a previous nephritis, one with tuberculosis, and three with diabetes. One case was reported with a history of hyperemesis gravidarum. There

was an antecedent history of eclampsia in one, and of preclampsia in four cases. Twelve patients gave a history of an antecedent hypertension, one patient gave a history of a hypertension, plus nephritis, and 16 patients gave history of a previous nephritis.

There were 6 patients who had been under our care twice and one patient who had been under our care three times.

So far as labor is concerned there were 13 previable deliveries. These were terminated by abortion in 5 cases, hysterectomy in 5, and hysterotomy in 3.

The onset of labor in 126 cases, or 48 per cent, was spontaneous, of which number 4 were previable, 35 premature and 87 at term. In 23 cases, or 9 per cent, the onset was by medical induction, of which number 10 were premature and 13 at term. In 58 cases, or 22 per cent, the onset was by mechanical, or medical and mechanical induction of which number 22 were premature and 36 at term.

The termination of labor in 136 cases, or 52 per cent, was spontaneous. Of this number 4 were previable, 44 premature and 88 at term. Sixty-five cases, or 25 per cent, were terminated by forceps, of which 1 was previable, 11 premature, and 53 at term. There were 6 cases terminated by version, 5 premature and 1 at term. There were 46 patients, or 18 per cent, who had cesarean sections. Of these cases there were 2 previable, 25 premature and 19 at term. Hysterectomy was done in 5 cases, hysterotomy in 3 cases, and craniotomy in 1 case.

There were 217 babies born and discharged alive, of which number 65 were premature and 152 at term. There were 21 antepartum fetal deaths, 6 previable, 9 premature, and 6 at term; 10 intrapartum fetal deaths, of which 3 were previable, 4 premature, and 3 at term; and 13 postpartum deaths, of which 1 was previable, 10 were premature, and 2 at term.

Consideration of the causes of these fetal deaths and autopsies will be referred to later.

No routine and extensive study of the placentas in these cases was made. There were, however, 13 cases of abruptio placentae, or 5 per cent, which is very much above the usual incidence of this complication. Placenta previa occurred once; retained infarcted placenta also occurred once. Degenerated, macerated and discolored, and autolytic placentas occurred once. There was one syphilitic placenta, and markedly infarcted placentas were recorded in 23 instances. The percentage incidence of degenerative changes in the placenta is not accurate as thoroughgoing study of these placentas was not done.

The febrile morbidity in these cases is strikingly large. Our ordinary morbidity, based on the standard of 100 degrees plus, occurring once in the puerperium, is less than 33 per cent.

The rise in temperature of from 100° to 100.8° was noted in 21 cases, or 8 per cent; 101° to 101.8° in 55 cases, or 21 per cent; 102° to

102.8° in 50 cases, or 19 per cent; 103° to 103.8° in 47 cases, or 18 per cent; 104° to 104.8° in 8 cases, or 3 per cent; 105° to 105.8° in 10 cases, or 4 per cent; and 107° in one case. The total febrile morbidity, based on temperature rise to 100° F., or more, was 74 per cent in this series.

In this series of cases there were four maternal deaths:

CASE 1.—Mrs. S., aged thirty-five, gravida iv. This patient had a marked hypertension and was delivered by hysterotomy, with sterilization, on Sept. 24, 1932. She was discharged from the hospital on Oct. 27, 1932, but her condition remained poor. She returned to the hospital Nov. 19, 1932, with severe headache, excessive vomiting, and loss of vision. She died of uremia on Nov. 25. No autopsy was permitted.

CASE 2.—Mrs. B., aged thirty-nine, gravida x. This patient had a persistent hypertension. She was delivered in the thirty-third week of gestation, following drug induction of labor. She had a partial abruptio placentae, but had a living premature infant. She died of uremia with congestive heart failure. Autopsy showed a chronic glomerulonephritis.

CASE 3.—Mrs. N., aged twenty-six, gravida ii. This patient was admitted to the hospital on Jan. 11, 1931, and on January 13, at the thirty-fifth week of gestation, after spontaneous onset of labor, was delivered spontaneously of a premature infant, which was born alive. This patient had a preeclamptic toxemia and acquired an antepartum infection, with a fever of 102° F. during labor. The infection was due to an anaerobic streptococcus. The patient died March 26, 1932, from puerperal sepsis.

CASE 4.—Mrs. C., aged thirty-six, gravida vi. This patient was admitted to the hospital on Jan. 30, 1932, and was delivered by low cervical section on Feb. 5, 1932, at thirty-one weeks' gestation. Death occurred the following day. This patient suffered from marked anemia, cardiac decompensation and hypertension. The autopsy findings substantiated the following diagnosis: Anemia, congestive cardiac failure, rheumatic mitral endocarditis, chronic nephritis with arteriolar sclerotic changes in the kidney, and acute toxic changes in kidneys and liver.

During this same period of time there were two deaths from convulsive eclampsia in the Chicago Lying-in Hospital.

In all, there were 44 fetal and infant deaths. Nearly one-half of these were antepartum. The antepartum deaths were due to various causes. Some were macerated; others showed signs of asphyxia, due in some instances to abruptio placentae.

The intrapartum deaths were mainly due to intracranial injury or suffocation.

The postpartum deaths were due to congenital deformities, to pneumonia from aspiration, and results of birth trauma. Many of these deaths were due mainly to prematurity.

One may conclude that, in institutions furnishing prenatal care, there are fewer deaths from convulsive types and relatively more in association with nonconvulsive types of toxemia.

The nonconvulsive types of toxemia seem to fall into two main groups, one in which the symptoms develop rather abruptly in the later months of pregnancy, reach an acme at the time of labor and, subsequently, tend to recede rather rapidly.

In the other type symptoms may be manifested early in pregnancy and become progressively worse as the pregnancy advances. These patients also reach a climax, usually in the later months of pregnancy, though this may occur in the early months of gestation.

There is very slow retrogression of symptoms following delivery and, while there is some improvement noted, the patients return to normal very slowly, if at all. These patients may die during the pregnancy, from impaired cardiovascular renal function, or may live, carrying damage to their heart, blood vessels, and kidneys, which may lead, ultimately, to their death. The important symptoms and findings in the clinical diagnosis of these conditions are well known and need not be repeated here.

Repeated pregnancies do serious damage, especially to the second clinical group, and should be avoided by sterilization of these patients wherever the severity of the condition warrants such a procedure.

Previous infectious diseases which damage the kidneys, heart, and blood vessels seem to be rather prevalent in this type of condition. These patients seem to be particularly inclined or susceptible to infection, as indicated by the high incidence of a febrile morbidity.

The maternal deaths and autopsies in this group of patients show the ultimate danger of deaths due to chronic and progressive changes in the cardiovascular renal systems. The treatment of these conditions is, mainly, prophylactic, and while one must probably recognize that many of these conditions are progressive in the individual, that they are, as a rule, seriously aggravated by successive pregnancies. The so-called preeclamptic and eclamptic condition may be regarded as one of greater immediate but less ultimate seriousness than the hypertensive and renal group. Clinically, it is often difficult to differentiate these conditions from one another, unless the patient is followed closely during pregnancy and the postpartum and subsequent period, for some time.

This emphasizes again the importance not only of prenatal care, but of postnatal follow-up. It is very important, but often difficult, to secure adequate cooperation of patients in order to obtain this necessary care for our maternity patients.

5848 Drexel Avenue

COMPARATIVE STUDIES OF THE BLOOD IN THE NONCONVULSIVE TOXEMIAS OF PREGNANCY*

WILLIAM J. DIECKMANN, S.B., M.D., CHICAGO, ILLINOIS

(From the Department of Obstetrics and Gynecology, The University of Chicago, and the Chicago Lying-In Hospital and Dispensary, and the Department of Obstetrics and Gynecology, Washington University School of Medicine, and the St. Louis Maternity Hospital)

MANY reports of the various chemical constituents of the blood in normal and abnormal pregnancy have been published, and the opinion expressed by many obstetricians is that there are either no changes of any significance or that chemical analysis of the blood in the toxemic patients is valueless. Many of these men follow such a remark or statement with a discussion of the merits of prenatal and postnatal care, in which they stress the importance of diet, vitamins, calcium, phosphorus, and iron—all of which have to do with chemistry. Furthermore, none of these men question the importance of hemoglobin studies in pregnancy and the prevention or treatment of anemia, which is not a question of how many erythrocytes does the patient have, but how much hemoglobin—a chemical compound—is there? Practically all of the reports are based on a *single* analysis of the blood of each patient, some being taken antepartum, some intrapartum, and others postpartum. A tabulation of data obtained under such diverse conditions will necessarily show wide variations, and the mean, if enough determinations have been made, will be approximately normal.

We have obtained one or more determinations on almost every toxemic patient, but are using for analyses 162, on whom at least two determinations were made, one of which was within one week antepartum and the other a similar period postpartum. The average number of blood analyses per patient was four, with a minimum of two and a maximum of 18. Much of these data had been collected prior to 1930, when an attempt at analysis was given up because the normal changes in the different constituents, incidental to pregnancy, had not been determined in the *same* women throughout pregnancy and the puerperium. This work has been completed since then and forms the standard to which the changes found in the nonconvulsive toxemias are compared. As complete an analysis as feasible, with the personnel furnished, was made on each blood specimen, and no attempt was made to prove or to

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disprove preconceived ideas or theories. In addition to the chemical examination of the blood, studies of the urinary chlorides, nitrogen, ammonia, phosphates, inorganic ash, etc., were made, which are also of significance but will be reported in a separate paper. Various renal function tests were tried and a large amount of data on these toxemia patients have been collected; and although they form no part of the present paper, we were influenced by the chemical analyses of the urine and the renal function tests, again determined both antepartum and postpartum, in classifying our patients.

* * * * *

We are reporting data obtained from 49 preeclamptic patients, of whom 34 are classed as severe, and 15 as moderate. The nonpreeclamptic group is composed of 113 patients, of whom 64 are severe, and 49 are moderate. We classified these patients as follows:

First, we separated them, according to clinical findings, into preeclamptic, designated "P," and not preeclamptic, designated "N" (nephritic toxemia and essential hypertension). On examination of the chemical data of each group we noted that the changes in the preeclamptic patients resembled those of normal pregnancy and especially eclampsia. Pregnancy is characterized by a labile blood and plasma

TABLE I. CHANGES IN THE BLOOD IN NORMAL PREGNANCY AS DETERMINED ON THE SAME PATIENTS

	NUMBER OF PATIENTS						
	ANTEPARTUM DAYS			POSTPARTUM DAYS			
	10-15	26-35	36-TERM	2-6	10-15	18-26 (8 WEEKS)	
Blood volume c.c. kg.	77.0	80.0	81.0	77.0		77.0	82.0
Plasma volume c.c. kg.	47.0	50.0	50.0	50.0		50.0	49.0
Hemoglobin gm. per 100	13.6	12.5	13.0	12.1		11.9	12.5
Hematocrit %	39.6	36.9	38.3	36.0		37.7	38.2
Erythrocytes—millions	4.45	3.88	4.25	3.87		4.12	4.44
Serum protein %	6.8	6.4	6.5	6.1	6.8	6.9	7.3
Fibrin %	0.40	0.43	0.48	0.55	0.43	0.42	0.43
Conductivity %	0.780	0.780	0.773	0.791	0.782	0.790	0.795
Total base mM.	154.6	152.2	150.6	152.9	153.5		158.0
Cholesterol mg. %	269.5	307.6	331.0	310.7	307.0	282.0	254.0
Nonprotein in mg. %	35.7	25.1	25.6	26.5	28.2		26.0

volume, by changes in the serum protein, conductivity, hemoglobin, fibrin, cholesterol, nonprotein nitrogen, etc. In Table I are listed the averages for these various substances for the different periods of normal pregnancy and the puerperium, as determined on the *same* patients. These changes are intensified in preeclampsia and eclampsia, thus giving further evidence of their intimate association with pregnancy. In preeclamptic patients there is a marked further decrease in these various constituents after delivery, which occurs coincidental with the negative water balance, but it is not proportional to the edema. Furthermore, we have seen these same changes without delivery, but with death of the

fetus, and two weeks later have noted a negative water balance and loss of edema but without any change in the blood constituents. Thus, these changes are fundamental ones associated with pregnancy and are not merely the result of delivery with its blood loss, anesthesia, or lactation, etc. The N-group shows no marked changes in hematocrit and serum protein either during pregnancy or the puerperium. If we had some accurate method for determining the blood volume daily, much valuable information could be obtained, but since such a method is lacking we used changes in hematocrit and serum protein as criteria for changes in blood volume. Each group was subjected to a careful clinical and chemical analysis. The latter, comprising a decrease in serum proteins of approximately 18 per cent together with a decrease of 15 per cent or more in the hematocrit in the P-group, required slight changes in classification. The proteins usually decreased well below 6 per cent, which was taken as the critical point. That is, if all the results were above 6 per cent, unless there were fluctuations of 18 per cent or more, the condition was considered one of nephritic toxemia or hypertension.

To simplify the laboratory diagnoses we multiplied the hematocrit by the serum protein, designating the resultant product "H·P." In eclampsia and preeclampsia the H·P, either before or after delivery, decreased well below 200. In a few cases it remained above 200, but showed variations of 100 or more after delivery. These patients were also diagnosed preeclampsia. The N-group showed much less variation of H·P and it did not go below 200, thus indicating that the serum proteins and hematocrit are more stable in this group and do not show the marked variations, especially the decreases observed in the P-group. In patients with anemia (low hematocrit) the H·P method of classification is useless, and one must disregard the cell volume and rely on the percentage and variation or constancy of the protein. As finally classified, the P-group was composed of 39 primiparas and 10 multiparas, while the N-group was composed of 32 primiparas and 81 multiparas. The definition for the latter was one or more pregnancies of seven months' duration or longer.

* * * * *

Thus, we may conclude that the acid-base equilibrium in the nonconvulsive toxemias of pregnancy, excluding only those patients who have a nephritis of sufficient severity to cause a nitrogen and anion retention, differs from that of normal pregnancy only in that the changes are more marked. The condition, as in normal pregnancy, is designated one of compensated alkali or CO_2 deficit, and, most important, it is obvious that there is no acidosis requiring alkali therapy. Furthermore, none of these substances is changed sufficiently in the majority of toxemic patients to make their determinations of clinical value. If there is a severe nephritis, marked vomiting, dehydration or oliguria, de-

termination of the CO_2 content, and one of the following substances—conductivity, total base, or chloride—is indicated. Although the routine determination of these various substances is valueless, no adequate explanation has been advanced to date which will satisfactorily explain the decreases in the CO_2 content, conductivity, and total base.

* * * * *

Conclusions based on nonprotein nitrogen and nitrogen fraction determinations by Plass, Stander, Bunker, Harding, Cruickshank, Wetterdal, and their coworkers, and many others, are essentially the same as ours, which briefly is that the routine determination of these various substances is valueless.

* * * * *

In Table VIII are listed the data for serum protein determinations. It is evident that preeclampsia is characterized by a lower concentration of protein than either normal pregnancy or the N-group, and one which is not constant but varies widely. The serum proteins in the N-group are similar to those of normal pregnancy. The changes in the P-group may be as great as 40 per cent in twenty-four hours, without any blood loss. (Note the marked changes in Tables XII and XIII, as contrasted with XIV, XV, and XVI.) The rapid changes in serum protein are due to changes in the water content of the plasma. Whether this is caused by a primary change in the protein, in the P_H, or in the blood volume we do not know, but more and more attention is being given to protein determinations as the number of reports from various laboratories indicate that investigators are becoming cognizant of their importance. Thus, Peters and coworkers have published a number of papers on protein changes in various diseases, have described marked alterations in diabetic coma, and have correlated the clinical improvement with a decrease (hydration) in the concentration of the protein. Other investigators note the relationship between decreased concentration of serum protein, especially albumin, and the appearance of edema. The albumin-globulin ratio does approach unity in normal pregnancy and even becomes less in many of the toxemic patients, as demonstrated by Seitz, Eufinger, Eastmann, Plass, and our work, but there are several findings which are difficult to explain. The serum proteins in pregnancy usually contain sufficient albumin to give a theoretical oncotic pressure of at least 20 cm. of water, which Hartmann and others assume to be the critical point for edema, i.e., if the oncotic pressure of the serum protein is less than this edema is likely to form. In normal and toxemic pregnancy the edema forms with serum proteins of 6 per cent or more, but disappears when the serum proteins are 4 to 5.5 per cent, or they are definitely less than at the time when the edema formed. Oncotic pressure measurements have been disappointing in our hands, but the few which we have made were within normal limits. We believe that there is an intrinsic change in the protein itself which at one time causes

TABLE XII. F. P.—No. 6559

PRIMIPARA. POSTMATURE. TOXEMIA P-3. ANASARCA. ALBUMINURIA 1.9 %. CESAREAN SECTION (5000 GM. BABY). WEIGHT LOSS 22.6 KG.

	ANTEPARTUM DAYS						POSTPARTUM DAYS							
	64	50	45	11	1	3 HR.	1	2	3	4	6	10	20	60
Serum protein %					5.6	5.7	5.0	4.5	5.0	5.6	5.3	5.8	6.3	
Hematocrit %					40.0	38.0	36.0	32.0	34.0	32.0	30.0	31.0	37.0	
H·P product					227.0	217.0	178.0	142.0	170.0	179.0	159.0	180.0	233.0	
Conductivity % NaCl					0.765	0.785	0.775	0.776	0.732	0.753	0.762	0.763		
CO_2 volume %					44.0	43.0	50.0	50.0	55.0	56.0	56.0	53.5	55.0	
Blood pressure			150		240	140	210	165		160		140		130
			100		150	100	140	120		120		90		90

C. W.—No. 4996

GRAVIDA VIII, PARA VII, AGE 38. TOXEMIA P-3. ANASARCA. MULTIPLE PREGNANCY. INDUCED LABOR BY RUPTURE OF MEMBRANES

Serum protein %					5.3				4.8		5.5	6.9	7.6	6.6
Hematocrit %					28.0				28.0		29.0	37.0	39.0	30.0
H·P product					149.0				134.0		158.0	253.0	296.0	198.0
Weight kg.	89.0	90.0		108.0	109.0								68.0	70.0
Blood pressure	106	114		170	215				170		150		145	115
	60	60		95	110				95		80		80	75

it to hold water and at another to release it. This, of course, is a well-known property of protein caused by changes in P_H, but in vivo we have not been able to detect changes in P_H of sufficient magnitude to account for such changes, although when the serum proteins are at the minimum we do find a definite increase in the CO_2 content but no appreciable increase in the P_H. However, when we precipitate the proteins, more acid is required, which suggests that they are binding more base. We have been attempting to detect these changes in the serum protein by surface tension and viscosity measurements, but so far without much success.

In Table IX are listed data for hematocrit determinations. Here again we note a marked difference between the values for the two groups. The cell volume per cents are lower in the P-group, especially after delivery. This decrease is not due to a blood dilution, as a result of the loss of blood at delivery, because in many cases we see it antepartum. This decrease in hematocrit in the P-group is similar to that seen in eclampsia, which favors their common etiology. The hematocrit in the N-group does not show the marked fluctuation and especially does not show such marked decreases as the P-group. Individual cases show even more marked fluctuations if they are preeclamptic, but very constant and high values, if they belong in the other group (note Tables XII and XIII, as contrasted with XIV, XV, and XVI). These findings which are analogous to the changes in serum protein are not accidental or coincidental, but are fundamental alterations which are of great significance and will be considered more fully in the discussion.

In Table X are listed data for hemoglobin determinations. There are marked variations, but the majority of the values are below the normal (14.3 gm. per 100 c.c.), and this is especially true in the P-group where, on the second to the seventh day postpartum, the average is 10.6 grams. These low hemoglobin values indicate that venesections are dangerous and may explain the increased susceptibility of these patients to infection. Hemoglobin is a function of the hematocrit and would, therefore, vary directly with the latter. Thus, the higher and more constant hematocrit in the N-group would indicate a higher and more constant hemoglobin, which is what is found. The frequency table indicates strikingly the greater number of high hemoglobin values in the N-group. Patients with a marked nephritis of long standing usually have a low hemoglobin, but the majority of the patients with nephritic toxemia, the acute phases of which are of relatively short duration, have normal or high hemoglobins. In the N-group the hemoglobins under 10.0 gm. were found only in those patients with a very definite nephritis of long standing and of sufficient severity to cause some nitrogen retention.

In Table XI are listed the H·P product data. It is obvious that the figures for the averages are much smaller, that there is much more fluctuation, and that there are many more low figures in the P-group.

TABLE XIV. D. S.—No. 72880

PRIMIPARA. THIRTY-SIX WEEKS' GESTATION. TOXEMIA N-2. SPONTANEOUS DELIVERY AT TERM

	ANTEPARTUM DAYS							POSTPARTUM DAYS							
	30	28	20	6	3	2	1	1	2	3	4	5	7	10	16
Serum protein %	6.4	6.9	7.4	7.7		7.5	6.9	6.3	6.5		7.1		7.9		
Hematocrit %	39.0	42.0	44.5	44.5		43.0	40.5	38.0	39.0		40.0		42.0		
H·P product	249.0	288.0	328.0	341.0		324.0	273.0	238.0	252.0		285.0		330.0		

A. V.—No. 78839

GRAVIDA XII, AGED 34. TWENTY-FOUR WEEKS' GESTATION. TOXEMIA N-3. HYSTERECTOMY

Serum protein %				6.7		6.9	6.6		6.2	6.0		5.9	6.4	6.9
Hematocrit %				38.0		38.0	42.0	40.0	40.0	39.0	39.0	39.0	39.0	38.0
H·P product				255.0		263.0	274.0		248.0	234.0		229.0	250.0	262.0
Hemoglobin gm.				12.4		12.1	13.0	12.0	12.6	13.2	13.0		12.3	
Conductivity % NaCl						0.776	0.772		0.806				0.790	0.786
Blood pressure				230		244								190
				140		134								110

Thus, after delivery 17 per cent of the figures are in the 100 to 139 series, while there are none in this range in the N-group. In the P-group, 31 per cent of the figures are less than 180, but in the N-group only 1.4 per cent are less than 180. We believe that a study of the serum protein and hematocrit demonstrate beyond question that there is a fundamental difference in the behavior of the blood and plasma volumes between preeclampsia, nephritic toxemia, and hypertension. As our data indicate, no attempt was made to collect data to prove such a theory, because if we had we would have obtained blood specimens on the proper days, and our results would be even more striking than they are. We have made no attempt to separate essential hypertension in pregnancy from nephritic toxemia, primarily because the end-result is usually the same, i.e., at autopsy the kidneys show the lesions of nephritis. It seems to us that the issue has been confused by the attempt at too fine a classification with too little criteria for the differentiation. Until we know more about the respective conditions, we prefer to group them into preeclampsia and nephritic toxemia, and in the latter condition to state that the lesion seems to be predominantly vascular or renal.

* * * * *

There may be some significance in the figures in that they indicate the direction of change, but blood volume determinations in pregnancy can be compared only if done on the *same* patient. Because of inherent difficulties in the method, we could not measure the volume as often as we could determine hematocrit and serum protein. In preeclampsia the blood volume is apparently increased, except when the symptoms become acute or the patient is in labor; then a concentration occurs which may be relative, if it is compared with the normal values for pregnancy, or absolute. Although all of the patients in the P-group had the initial determination while in labor, the blood and plasma volumes after delivery were either decreased or showed no change. However, one patient who later developed a very severe eclampsia had an increase of 1,000 c.c. above the initial blood volume when examined at eight weeks' postpartum, indicating that the antepartum volume was below normal. Another patient, who subsequently died, had a very marked increase in blood and plasma volumes, coincidental with clinical improvement. In the N-group 4 patients showed an increase in volume after delivery, 1 showed no change, and 10 definitely had less blood and plasma at three to eight weeks postpartum (note Tables XV and XVI). No definite conclusions are warranted.

* * * * *

DISCUSSION

Physicochemical studies of the blood in the toxemias of pregnancy have revealed marked and fundamental alterations in many of the important constituents. We are not prepared at present to explain these changes, but believe that proper studies will eventually lead to an under-

standing of the different types of toxemia and will solve the enigmas of edema and hypertension. The toxemias of pregnancy are ideal cases in which to study these problems because the entire cycle is covered in a period of months, and usually the return of all conditions to normal furnishes its own control, whereas the internist must wait years for the cycle to be completed in the case of nephritis and hypertension.

Our studies, as well as those of other investigators, have been extremely disappointing in having any clinical value, not because there were no marked changes, but primarily because we could not coordinate them with the disease. Thus, a serum protein determination before delivery and one two weeks postpartum would probably be the same, but there have been marked changes in the interval that, although we cannot explain them, can be correlated with the clinical condition and may be used as criteria on which to base a diagnosis and prognosis.

Blood volume determinations at present cannot be carried out at short intervals; therefore, we have to rely on serum protein and hematocrit determinations, assuming, justifiably, that changes in these substances represent changes in blood and plasma volumes. We do not propose now to discuss which one is primary. The increase in blood, and especially plasma volume, has been noted by many observers since the first description by Nasse in 1876. Zangemeister and Plass have demonstrated that there is a dilution of the blood in toxemic patients, especially after delivery, and that it is accompanied by the abatement of the symptoms, but these observers concluded that the phenomena were coincidental and that the decrease in serum protein was due to and varied directly with the degree of edema. That is, the protein decreased because the water entered the blood stream from the tissues more rapidly than the kidneys could eliminate it, resulting in a blood dilution. There is no correlation between the amount of edema and the degree of decrease in serum protein or hematocrit. The changes are more fundamental because even with a continuous injection of Ringer's or glucose solution, provided they contain no colloids, the blood volume soon adjusts itself, returns to the normal, and then remains constant.

We were particularly pleased by the accidental discovery of an article by Skajaa, whose results are identical with ours. He determined the cell volume on venous blood, using heparin as an anticoagulant, and based his conclusions on *repeated* determinations during labor and the puerperium in 37 normal patients, 23 patients who developed albuminuria during labor, 22 patients with nonconvulsive toxemia, and 16 patients with eclampsia.

* * * * *

Changes in blood volume, especially concentrations, are found in diabetic coma, intestinal obstruction, shock, cholera, severe burns, and eclampsia—all conditions which are dangerous to life; therefore, a concentration of the blood is a fundamental change. Alterations in the

water binding properties of the proteins and in the capillary permeability, as in shock, are a factor, but what initiates these changes?

* * * * *

The marked changes in the hematocrit and serum protein in normal pregnancy and the toxemias are best shown by the averages listed in Fig. 1.

We have injected gum acacia solution intravenously into preeclamptic and eclamptic patients, and have noted that clinical improvement was always associated with a definite decrease in serum protein and hematocrit, produced by the presumable increase in plasma volume as a result of the introduction of the colloid. This dilution was usually maintained for several days, but in patients with nephritic toxemia we noted no change in the clinical symptoms and much less change in serum pro-

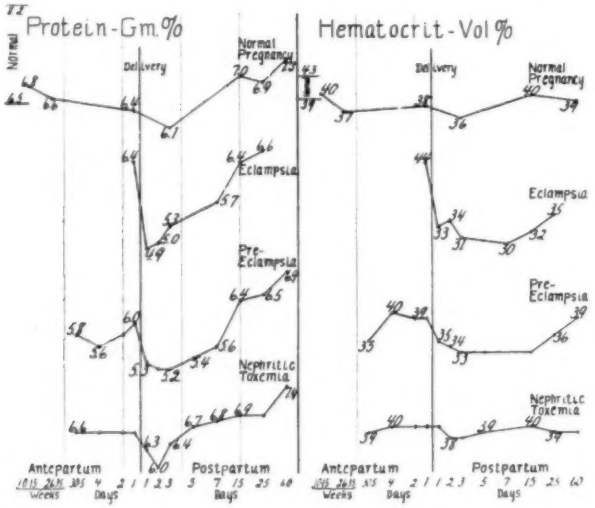

Fig. 1.—Average changes in serum protein and hematocrit.

tein and hematocrit, and a shorter duration of the decrease. Irving states that plasmapheresis is efficacious only in eclampsia and preeclampsia. It seems obvious that the entire mechanism of the body in these conditions must be different from that acting in nephritic toxemia.

To separate preeclampsia from nephritic toxemia we believe at present that determinations of serum protein and hematocrit at properly spaced intervals are of considerable value. Just as in all differential diagnoses, the history, symptoms, signs, and the various laboratory reports must be properly evaluated. Our technicians, knowing nothing of the patient's history, have made the proper diagnosis repeatedly, as they noted the change or lack of change in these substances, but again we wish to emphasize that the laboratory report, whether chemical or serologic, must be considered at present only as a part of the examination.

While many of the blood constituents show marked changes, for purposes of diagnosis, prognosis, and treatment, we suggest the determina-

tion of hematocrit (simple and accurate), serum protein (accurate but difficult), and hemoglobin (accurate but more variable) before delivery, from forty-eight to seventy-two hours postpartum, and again at two weeks. The blood must be obtained and analyzed properly if the results are to be of value.

The application of our clinical and chemical classification is best illustrated by the following cases:

Table XII contains data from 2 preeclamptic patients. F. P. is obviously a preeclamptic, but C. W., on admission, would be classed as a nephritic, and yet their behavior, both from the clinical and the laboratory viewpoints, is identical.

* * * * *

CONCLUSIONS

Physicochemical analyses of the blood in the nonconvulsive toxemias of pregnancy, to be of value, depend on proper methods for obtaining the blood, exact methods of analysis, and a recognition of the time in the pregnancy cycle when the specimen is taken.

The following conclusions are indicated:

The average for the serum chlorides is 593 mg. per cent, which is the same as in normal pregnancy, but the variations are greater in the toxemic patients.

The average CO_2 content of 51 volumes per cent is from 2 to 5 volumes per cent below that of normal pregnancy, and from 8 to 15 volumes per cent below that found in the nonpregnant person.

The minimum average serum conductivity of 0.740 per cent occurred in the preeclamptic group on the day of delivery. The averages in both groups were less than those of normal pregnancy, and the total electrolyte did not become normal until two or three weeks postpartum.

Total base differs from that of normal pregnancy in that the decreases are slightly greater.

The P_H remains within the normal range and the condition is one of a compensated alkali or CO_2 deficit. There is no acidosis requiring alkali therapy.

Nonprotein nitrogen, urea, uric acid, creatinin, and amino acids are within the range for normal pregnancy. Urea and nonprotein nitrogen are at the lower limits of normal, thus the undetermined nitrogen is increased. The averages for both groups ranged from 26 to 31 mg. per cent. Marked increases in any of these substances are rarely noted.

The averages for plasma total cholesterol in preeclampsia range from 382 to 234 mg. per cent, and for nephritic toxemia from 359 to 293 mg. per cent. There is no significant difference from that of normal pregnancy, but the figures are much higher than found in the nonpregnant woman.

The averages for plasma fibrin in preeclampsia range from 0.546 to 0.320 per cent, and for nephritic toxemia from 0.627 to 0.385 per cent. The maximum figures, similar to those of normal pregnancy, occur within the first week postpartum and not during pregnancy.

The averages for hemoglobin in preeclampsia range from 13.1 to 10.6 grams, and for nephritic toxemia from 13.5 to 12.3 grams. The variation of from 5.0 to 18.9 grams in both groups is marked. Preeclampsia is characterized by a lower and more fluctuant hemoglobin than nephritic toxemia. Because of this low hemoglobin, it is apparent why venesection is contraindicated and why these patients are more susceptible to infection.

The changes in the blood and plasma volumes are of maximum importance, but it is impossible to determine them directly. Serum protein, hematocrit, and hemoglobin determinations are exact and can be carried out repeatedly, and give indirect information as to changes in blood volume.

Preeclampsia is characterized by a labile blood and plasma volume, if we use serum protein and hematocrit determinations as the criteria. After delivery there is a marked decrease in these constituents, amounting to from 15 to 25 per cent. In particular, the serum protein, both antepartum and for the first week postpartum, is less than 6 per cent.

Nephritic toxemia and hypertension in pregnancy are characterized by a more stable blood volume, and after delivery the serum protein and hematocrit show much less, if any, fluctuation. The serum protein in the majority of these patients is above 6 per cent.

Repeated analyses at properly spaced intervals are of value in differentiating between preeclampsia, chronic nephritis, and essential hypertension. The optimum times for a minimum of three specimens would be before or early in labor, from forty-eight to seventy-two hours postpartum, and again at two weeks. Lack of fluctuation of serum protein of 18 per cent or more and of hematocrit of 15 per cent or more, would indicate that the condition is a nephritic toxemia or essential hypertension in pregnancy.

Pregnancy, whether normal or toxemic, offers the most suitable material for investigation to determine the cause and cure of edema and hypertension, because the changes, although marked, are usually of relatively short duration and particularly in many cases the recovery is complete.

METHODS

Serum protein, albumin-globulin ratio, and fibrin were determined with the interferometer. The serum was separated from the clot within twenty to forty minutes after venipuncture.

Conductivity was determined with the Wheatstone bridge of the Leed and Northrup student potentiometer, a microphone hummer as a source of high frequency current, resistance box, earphones, and a special 2 c.c. cell which could be sealed to

prevent loss of CO_2. All readings were made at 20° C. The instrument was calibrated with a known solution of NaCl, and checked on numerous occasions. The average of a number of readings was taken, and we believe that this measurement of serum electrolyte is far more exact than the determination of total base. Corrections were made, using the Gram formula for the depression caused by proteins.

$$C_c = \frac{C_o \times 100}{100 - (d \times p)}$$

C_o = observed conductivity as per cent of NaCl.
C_c = corrected conductivity as per cent of NaCl.
p = serum protein.
d = 2.2 − Gram's factor for depression caused by 1 per cent protein.

Hemoglobin was determined as carbon-monoxide hemoglobin, using from 0.2 to 0.5 c.c. of blood. The oxygen capacity of the standard was checked at weekly intervals.

Hematocrit was determined on heparinized blood in Plass hematocrit tubes.

Cholesterol was determined by Leiboff's method.

Standard procedures were used for all other determinations.

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5848 Drexel Avenue

NEPHRITIS AND PREGNANCY*

JAMES R. GOODALL, M.D., MONTREAL, QUE.

IN 1930, a young woman consulted one of my colleagues, having learned that she had kidney trouble and wishing to know the influence this might have on childbearing, as she contemplated marriage. She was then twenty-eight years of age. "She was a Canadian by birth, had had scarlet fever at two and a half years of age, measles in later years. She was employed as a stenographer. Her mother and father are alive and well, as are also two brothers and two sisters. All the functions seemed normal, weight 104 pounds, skin a trifle dull and pimply. Blood pressure 170/90, albumin +++, no casts. Three days later she was reexamined,—blood pressure unchanged and albumin +++, again no casts." He gave her a very bad prognosis as regards childbearing, and pictured a very black outlook as regards the outcome, just as you or I would have done. However, she got married, and her husband, who knew previously of her malady, sent her to another physician. This was in 1931. He found the blood pressure 185/100, a slight cardiac enlargement (?), a large amount of albumin and other clinical signs of nephritis, a few granular and hyaline casts. He sent her to the Montreal General Hospital for observation by himself and the clinical chemist of that Institution. The diagnosis of chronic nephritis was substantiated after a complete blood chemistry analysis.

About January, 1932, she became pregnant and was in a great fear. She went to see her doctor again as soon as she was certain of her state. He reexamined her, confirmed all the signs of nephritis, and sent her to me with a view to having a therapeutic abortion done. On examination I found the blood pressure 190/105, slight cardiac enlargement (?), no arteriosclerosis, fundi normal, a very large amount of albumin, a few granular and hyaline cases. Pregnant two and a half months. Her maternal instincts were so strong that she pleaded a trial, willing to undertake any risk for the fulfillment of her desire. I acceded unwillingly, and put her upon a very full protein diet for two weeks, with a promise given that if she was worse at that period, surgical intervention would be undertaken. Upon her return the albumin was less, the blood pressure had fallen to 160/90, and she felt remarkably well and determined to persevere. During the next month she slowly improved until June, 1932, at four and a half months, she had a blood pressure of 110/70 and there was only the faintest trace of albumin on boiling. There were no casts or blood elements in the urine. Her general condition improved as the months went by.

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In July, she was free from albumin, her blood pressure was 110/75, and she had gained fifteen pounds. At the end of the pregnancy she had gained twenty-nine pounds, "never felt better in her life," and was on a full diet throughout. The blood pressure never rose over 110 at any visit, and there was, from time to time, the merest trace of albumin, as the only indication that all was not normal. She had a long and rather difficult, but uneventful labor, with a normal child of six pounds fourteen ounces, a normal placenta, and an absolutely normal puerperium. This was in November, 1932.

I have seen her every month since then; the last time but a few days ago. She is the happiest of persons and is keen to have another child at once. Her blood pressure since delivery has never been over 120/80, usually 110/70 to 75. There is only the faintest trace of albumin occasionally, and I have never found any casts in centrifugal specimens. At present she weighs twenty pounds more than before her pregnancy.

There have been four other cases of a similar nature, in which the details are less complete; but all of them, except one, were sent to me by members of the Medical Staff of McGill with a diagnosis of nephritis after many months, in some cases years, of observation. Details of these will be given in a larger work, which I have under way. In all of these the patients' wishes for progeny had to be respected.

In one, a physician's wife and a graduate nurse, there had been all the signs of a chronic nephritis with an infarcted placenta and dead child born two years previously. When her husband brought her to me at the third month, her blood pressure was 175/100, the specific gravity was 115, and there was a trace of albumin and a few hyaline casts in the urine. In view of the past history, I gave a very bad prognosis. She went through the next months improving, until between the fourth and fifth months she had a normal blood pressure and a normal urine. There was a normal delivery, a normal child, and a normal placenta.

Now how can we account for these exceptional cases? In reality they may go a long way toward solving a very difficult problem. Here are cases which, by all the known clinical rules, should have undergone a great risk and aggravation of their kidney lesion, but instead show a marked improvement under the influence of pregnancy. The data of nephritis are indisputable, as are also the course of the pregnancy and its results. Do these cases throw any new light upon the subject of nephritis and eclampsia? Most decidedly, they do.

In 1922, I stated that the toxemia of pregnancy is of endocrine origin, and this I have repeated on many occasions in my writings. Hofbauer first stated this in 1918, and has maintained it ever since.

We all know the various theories for the explanation of the toxemias. Many of them, emanating from the knowledge that chloroform and phosphorus produce hepatic lesions somewhat similar to those of

eclampsia, have led to the theory that the toxemias of the second and third trimesters are due to a poison in the system, which acts like those of chloroform and phosphorus. And most of the research has been bent along two lines:

1. To the detection of a poisonous substance—probably a split protein—emanating from the placenta, or the fetus.

2. A metabolic upset originating with pregnancy, but affecting the mother's liver and excretory organs.

Now let us look at this question without bias. I will give you only opinions, leaving the reasonings which lead up to them for the larger work.

In the first place, on the one hand, there are women who are normal in the nonpregnant state, and toxic when in the last two trimesters of pregnancy and, on the other hand, I have quoted five cases of toxic, nonpregnant and first trimester pregnant women, who in the second and third trimesters become quasi-normal. What internal condition will explain this paradox? Have we any other consideration which approaches this state of affairs? Decidedly, yes.

Let us look at certain cases of thyroid instability. Have we not cases of thyroid dyscrasia which are decidedly aggravated by pregnancy? and have we not also a goodly number who are decidedly better of their hyperthyroidism during the pregnant state? I could quote case after case of both types. How do we explain this anomaly? It is very simple. It all resolves itself into the interaction of a stimulus (pregnancy), a changing consumption, and the reserve power of the gland or glands in question. In other words, an equation made up of stimulus, need, and response. A glance at the accompanying diagrams will illustrate my point.

But there are other glands of internal secretion more affected by pregnancy than is the thyroid. Before entering upon this phase of the subject, let us consider the functional and the organic changes which characterize toxemia of pregnancy.

Domagk has shown that in eclamptic patients without infection, there are endothelial changes in the liver, spleen, glomeruli, and lung capillaries, characterized by swelling of the lining cells of the capillaries and lymphatics, growth and multiplication and detachment of wandering cells, often to the degree of complete blockage of the capillaries and lymph channels. There is a host of minor intimal functional disturbances ending in edema, liver necrosis, cloudy and fatty degeneration of the kidneys, and a concomitant vast array of symptoms and signs culminating in eclampsia and coma.

Among these, of fairly constant occurrence, are elevated blood pressure, albuminuria, and edema. Now there is a wide difference between functional disturbance with minor reparable damage, which eludes

detection, and irreparable discrete organic disease. Sufficient emphasis has not been laid upon this distinction. In chronic poisoning, the body cells have time to accommodate themselves more or less to their new environment. The result is usually a dysfunction; later, a vitiated function leading to slow cumulative toxemia, and slow organic changes.

On the other hand, in acute fulminating conditions, the first stages of dysfunction and of vitiated function are too short to allow the body to meet the onslaught, and in its unprepared state, widespread organic destruction follows rapidly. This explains why it is that chronic toxemias rarely pass into eclampsia. For eclampsia is an acute disease, and the parallel, both as to capillary changes and other corporeal degenerations, and as to symptomatology and sequelae between acute and chronic infections on the one hand, and acute and chronic pregnancy toxemia on the other, is perfect.

Just as acute infections are rapid in onset, upsetting function and metabolism in proportion to their acuteness, so recovery is complete and usually rapid without appreciable after-effects; and contrariwise, just as chronic infections are slow in development and lead to functional and organic changes with a permanent damage, so we find the same conditions parallel in toxemias. Our present subdivision of toxic cases into chronic nephritics and toxemias is wrong. It presupposes that a chronic nephritis, often cryptic, precedes the pregnancy under observation, whereas in most instances the renal damage is in a state of development while the patient is under observation. True, a percentage of them have had a damaged kidney from some antecedent disease, or from an antecedent pregnancy, but the chronic toxemia of the pregnancy under observation is the all-important injurious factor, whether it be an added organic disease or the first organic renal change.

Ordinarily we teach—and I have been equally guilty of this differentiation—that there is but one toxemia of pregnancy, the preeclamptic; the other class we denominate nephritis complicated by a pregnancy, whereas in most instances, it is the same pathologic process under a different form of intensity. The cases in which it is possible to diagnose a nephritis, antedating the pregnancy, are relatively rare. In all the others we are unable, except by a history of former toxemias, to determine how much renal and other epithelial damage and permanent functional derangement dates from an antecedent cause, and how much is due to the present toxic state of the patient. We may now summarize by stating that the damage due to the toxicity of a pregnancy, will be equal to those clinically appreciable factors, the *intensity* multiplied by the *duration* on one side of the equation, and the *instability*, the *supersensitiveness* and the *reserve* of the renal, hepatic, vascular and cerebral, and the glandular systems on the other. The importance of this will appear later. Having laid down these

premises, let us attack the subject more closely. The dominant signs of toxemia are: Elevated blood pressure, edema, albuminuria, coma, and convulsions. These will be dealt with separately.

The chief changes in the material organization in pregnancy must be looked upon as of internal secretory origin. We know of the increased functions of the ovary, of the anterior pituitary, and of the thyroid. In pregnancy the whole inner secretion undergoes a marked hyperfunction, but a hyperfunction that is a demand and a fine neutralizing balance, in marked contradistinction to secretory disease. In normal cases this normal hyperfunction is so coordinated and balanced that in the end it does not affect metabolism, circulation, or nerve excitability. True, during the orderly course of the life processes and the subjective and objective well-being of the pregnant woman, this balance is maintained. But it is equally true that the increased activity of the secretory system in many points in the pregnant woman leads to departures from the condition in the nonpregnant state which we recognize as the work of now this, now that, gland.

Hofbauer was the first to implicate the posterior lobe of the pituitary and the adrenal, in the production of the nephropathies of pregnancy and eclampsia. Hofmann and Anselmino have since shown, within the last two years, that the nephropathies of pregnancies and eclampsia arise out of a secretory dysfunction, a dysfunction which is frequently pluriglandular, but in which the uncompensated overproduction of the posterior lobe of the pituitary dominates the picture.

It has been known that with the use of old-type pituitary extract, injection of this substance causes an inhibition of diuresis and a rise in blood pressure in healthy persons.

There are probably many components of the posterior lobe extract, but four with characteristic physicopathologic actions have been isolated. These are: (1) A stimulant to unstriped muscle (oxytocin), (2) a melanophore dilating substance. (The action of this substance on the frog is well known, but that upon human beings is not known), (3) a water-retention or antidiuretic principle, and (4) a blood pressor.

Old commercial preparations contain all four of these known ingredients. But for a comparatively long time the whole extract has been split into oxytocin and hypophanin or tonephin. The former contains as its chief component No. 1 of the above list, and the latter contains chiefly Nos. 3 and 4.

In 1929, Draper split the latter half (hypophanin or tonephin) into its two components, the antidiuretic principle and the pressor factor. This was confirmed by Heller one year later. In the blood of clinically normal nonpregnant women, and clinically normal pregnant patients, it is impossible to demonstrate either of these two substances in the blood. But with the blood of nephropaths of pregnancy and

eclamptics, the antidiuretic is consistently demonstrable, whereas the pressor substance is demonstrable only in cases in which the blood pressure is over 180.

It is to the credit of Hofmann and Anselmino that extracts of these two substances taken from the blood of nephropaths and eclamptics have been obtainable, and their physicochemical action demonstrated to be similar in every detail to extracts obtained direct from the posterior lobe. It would seem that their work upon rabbits, with controls,

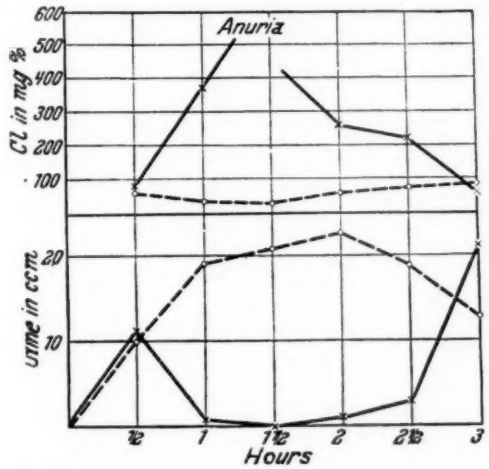

Fig. 1.—From Hofmann and Anselmino, showing curves of urinary secretion in injected animal and control. In the upper section the control and injected rabbit's chloride excretion.

---- control:—injected animal.

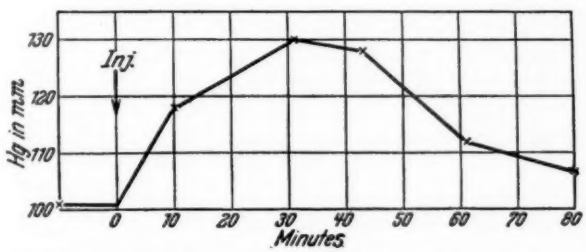

Fig. 2.—From Hofmann and Anselmino, showing rise in blood pressure in injected rabbit.

shows a monotonous uniformity of reactions that places the antidiuretic content of the blood of these cases beyond any doubt. The pressor substance, on the other hand, is present only in cases of markedly high blood pressure of 180 systolic or over. Under this pressure this reaction in animals is absent or doubtful.

These substances are not free in the blood, but are held in combination with the protein molecules, and when the pure hormone is injected in combination with a protein, it loses a great deal of its effect, showing that a large part of the hormone is held in a protein combination.

Dudley, Abel and Guggisheim and others demonstrated that the hormone is extraordinarily sensitive to alkalies and stable with acids.

Doubtless the inability to demonstrate the pressor substances in nephropathies with a blood pressure below 180 mm. Hg may be explained, in that it operates in infinitesimally small quantities, but that the quantity increases markedly as the pressure rises. In other words, increasingly larger amounts are necessary to increase the blood pressure as the pressure rises. So that clinically 10 mm. of rise between 120 and 130 could be effected by a minimal dose, but a similar rise at 180 or 200 mm. would require extremely large doses. By this we can judge of the clinical importance of the high blood pressures.

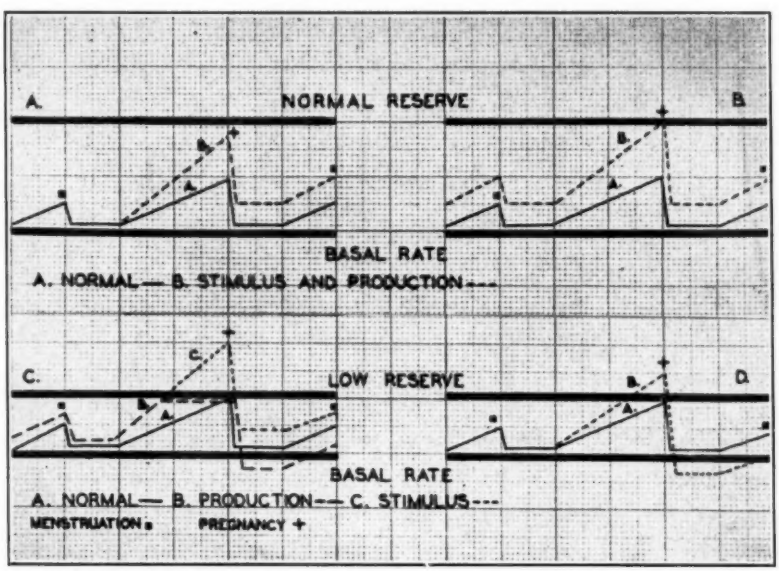

Fig. 3.—*A* represents schematically a normal thyroid menstrual and pregnancy reaction. Contrasted with an overstimulation and overproduction of pregnancy. This case will exhibit symptoms of hyperthyroidism in the pregnant state; normal gland reserve.

B.—A normal thyroid curve, and one of hyperthyroidism before, during, and after pregnancy; a normal gland reserve.

C.—A case of low gland reserve. A normal tracing, contrasted with a prepregnancy hyperthyroidism, and an inadequate response to a pregnancy stimulus. This results in improvement during pregnancy with a return to (first) the status quo ante or (second) to a normal thyroid activity or (third) to a hypothyroid state consequent upon gland exhaustion.

D.—A case of low gland reserve, sufficient unto the needs of the nonpregnant state, but resulting in athyrea during pregnancy and a postpregnancy normal or athyreic state.

In the accompanying diagrams, I have reproduced the oft-repeated tests of Hofmann and Anselmino, in the first, demonstrating the effect of the injection subcutaneously of 10 c.c. of the blood extract, and the curve of the control rabbit which received a quantitatively similar injection of fluid similarly treated with acid and neutralizing substance. The curve of chloride excretion and the curve of urinary secretion are shown graphically. I shall have occasion to revert to these later.

In the second diagram are shown the curves of rabbits similarly treated with the pressor substance from a patient with a blood pressure over 180.

Now an interesting sequel, and one which is in conformity with the expected, is that the products of superactivity of the posterior lobe, the antidiuretic and the pressor substances, are rapidly eliminated as soon as diuresis sets in postpartum. This arrest of overproduction and elimination of excess by diuresis also ordinarily takes place upon the death of the fetus, but it does not occur in cases of postpartum eclampsia or in cases of vesicular mole. The incidence of eclampsia at the fourth and sixth months of pregnancy, where, of course, the fetus has died long since, is a potent argument that the internal gland excitation of pregnancy finds its stimulus in placental activity.

Let me repeat that these experiments were done on numerous sick persons and normal controls, and always with control rabbits, and the graphic reactions reappear with amazing, even monotonous, regularity. Now, what is the clinical bearing of this gland dystrophy?

If we apply the diagrams descriptive of thyroid activity relative to pelvic functions to the functions of the posterior pituitary lobe under similar conditions, we find that a great many heretofore inexplicable phenomena become crystalline clear.

Normal posterior lobes with normal reserves respond as do the other glands to the normal stimulus of pregnancy. On the other hand, glands of normal stability and low reserve cannot meet the demands, and the consequences are hypopituitary states during pregnancy with low blood pressures, low uterine contractility, low muscle-nerve irritability, etc., and unstable glands that are in a state of hyperfunction before pregnancy and, having a normal reserve, may respond too vigorously with all the consequences of antidiuresis, high blood pressure, albuminuria, nephropathies, liver necrosis, and all the symptoms which accompany these states. If you revert to the diagrams on thyroid dysfunctions in pregnancy, you will see that the parallel is perfect. Moreover, it has been clearly demonstrated that the pressor substance of the posterior lobe and the antidiuretic substance operate independently, so that in one case the one may predominate, producing high blood pressure, urine of low specific gravity, capillary contraction with capillary internal changes, and a resultant cardiovasculo-renal dysfunction, which if prolonged and of greater intensity leads to permanent, irreparable organic disease; or, if the antidiuretic substance dominates the picture, we find scanty urine filled with albumin and casts, edema, and vascular changes—first dysfunction, later liver necrosis, eclampsia, and coma.

A glance at Fig. 3 on thyroid dyscrasias shows that hyperthyroidism antedated the pregnancy, and that improvement took place during the pregnancy owing to the lack of response to the pregnancy stim-

ulus. The low reserve of the thyroid was the cause of the inadequate response, and the increased need for thyroid secretion during the pregnancy used up the previous excess. At the height of the pregnancy demands, there would then be a relative and absolute hypothyroidism, and the postpartum effect upon the thyroid activity would depend upon the degree of exhaustion of that gland. So it is in my cases; they were all hyperpituitary dyscrasias before pregnancy, and their response during and after pregnancy is analogous in every respect to similar cases in thyroid instabilities.

What clinical evidence have we that this is sound clinical research?

1. To the best of my knowledge there are only two glands of internal secretion that possess pressor action; they are the posterior lobe of the pituitary and the adrenal. Probably in many cases of toxemia the two are involved simultaneously, for I stated at the beginning that the condition is often pluriglandular.

2. Posterior lobe injections have been used with success to inhibit the excessive urinary secretion of diabetes insipidus.

3. At the menopause it is common to find a high blood pressure, casts, and albuminuria with intermittent glycosuria, which may last for a very considerable period, and then disappear, leaving no appreciable trace of its nefarious work. Undoubtedly this pressor state is due to posterior lobe or adrenal instability due to ovarian withdrawal. But the condition adjusts itself with time.

4. It offers a ready explanation for the five cases which I am reporting of excessive pressor secretion, which the pregnancy cellular demand consumes. If we assume, as in thyroid cases, that the posterior lobe could not respond to the full stimulus of pregnancy, then the previous excess would be used up by the pregnancy metabolism, and the subsequent postpartum state of the gland, whether of renewed vigor or of exhaustion, would determine the improvement, or not, of the previous nephropathy.

5. It offers also ready explanation for the chronic toxic cases and the acute fulminating ones, and readily accounts for the consequences of each in their aftermath.

6. It offers a ready explanation for the rapid recovery of the patient as soon as the inhibition of the diuresis is removed, and renal function sets in with increased output, and when the source of the stimulus to overproduction (the pregnancy) is removed. It also has been shown that in cases of postpartum eclampsia, the excess of posterior lobe still persists in the blood after labor, due to remnants of placenta being active, or to delayed elimination by the kidneys, or to delayed action of the internal secretion, or to a combination of these causes. It explains readily that the cause of the water-retention is not to be found in the organic disease of the kidney; the kidney lesion is a resultant

of the internal secretory dysfunction with the metabolic poisoning. Otherwise, renal function could not be reestablished so readily, when the overproduction is arrested, if the renal organic disease was the cause of the edema.

The kidney lesion must be looked upon as primarily functional, becoming organic only after long duration of metabolic upset, leaving behind in the milder cases a lowered reserve in kidney function, but a reserve above ordinary daily needs; or, in more damaged cases, a cryptic nephropathy, detachable only under strain, such as a subsequent pregnancy; or, in more severe cases a permanent, detectable, vitiated function.

7. It explains the modus producendi of the mild metabolic dysfunction and the more marked organic destructions which occur in toxemia, for, let it be clearly understood that the under- or overproduction of any gland does not lead to these destructive changes that one finds so prevalent in kidney, spleen, liver, and other organs of toxemic cases. The hypo- or hyperfunction of a gland of internal secretion first operates upon the human organism by deranging function in proportion to the intensity of the glandular defect coupled with the supersensitiveness of the individual concerned, and upon these two factors hinges the whole truth of the toxemias. The vitiated function may be acute or chronic, depending upon the two above-mentioned factors. In the chronic cases the body cells and fluids have time to adjust the situation to the best of their reserve, drawing upon other glands to neutralize or inhibit, building up antebodies, etc., but the deleterious agent in all this is the vitiated metabolism, which, if acute, leads to the destructive changes enumerated above without the intervening stages being apparent to the clinician. But in the chronic stages these are slow and, though apparent, are more or less insidious. Even to those who are not conversant with the importance of internal secretion to metabolism, it requires no great stretch of the imagination to picture the ravages of disruption of bone metabolism as seen in osteomalacia, or the inordinately startling symptomatology sequential to a calcium unbalance due to parathyroid dyscrasia. These are all small beginnings with frightful consequences, and the only inference justifiable is that the study of the metabolic changes incident to toxemic conditions in pregnancy is that it will lead to a better understanding of primary and secondary consequences, but not to an understanding of the primary causes.

For let it be clearly understood, and this is the very crux of the situation, that gland dystrophy, whether it result in hyper- or hypofunction, does not in itself produce the organic lesions of which we have such ample evidences in medicine. This is not their modus operandi. Gland dystrophy first manifests itself in a disturbance of the nor-

mal metabolic functions over which it normally exercises a controlling influence. For example, in pancreatic disease, the body becomes poisoned by the vitiation introduced into the sugar balance. The consequent diabetes, diabetic coma, acidosis, and the associated organic lesions, are due primarily and indirectly to the pancreatic dysfunction, but secondly and directly to the vitiated metabolic toxic state. And so it is with the other glands; thyroid dystrophy may cause cell activity to lose all sense of normal proportion, a slight disturbance in the supply of the parathyroids causes an imbalance in the economy of the ions of calcium and phosphorus, with its clinical consequences of deranged coagulability, hemorrhagic states, hyperexcitability of nerve-muscle reaction, and finally tetany. It now becomes evident that gland dystrophy per se does not affect the body economy directly, but affects the organic structures directly through disturbed metabolism.

To spend great effort upon the metabolic and organic changes will prove as remote and futile in disclosing the cause of the disease, as would the study of the cardiovascular-renal effects in thyroid dyscrasia.

One of the first consequences of the antidiuretic action is to prevent excretion of urine. But with this, the chlorides are excreted in the urine in enormous quantities, as seen in Fig. 1. These excessive chlorides have to be neutralized in the urine by the withdrawal of bases from the blood and tissue-plasma alkalies, thereby causing alkalipenia of the blood. The resultant also is an accumulation of acids in the blood and a condition of general acidosis. Clifford White very clearly states that "it is a popular idea that the acids of acidosis circulate in the blood." This is not the case, as, even in the most extreme cases of acidosis, death occurs before any gross alteration takes place in the reaction of the blood, which normally is slightly alkaline from the presence of protein and of carbonates and phosphates. This alkalinity is maintained in spite of the fact that on a mixed diet, there is a production of acid bodies from the metabolism of carbon, phosphorus, and sulphur. This tendency toward acid formation is corrected both in health and disease by oxidation, excretion, and neutralization.

1. *Oxidation.*—Carbon is oxidized and then excreted as CO_2 by the lungs or as urea by the kidneys.

2. *Excretion.*—In addition to getting rid of the products of partial or complete oxidation, the kidneys maintain equilibrium by their property of excreting a normally acid urine from a normally alkaline blood. This is done largely by the excretion of acid phosphates, such as NaH_2PO_4. It will be noted, however, that before excretion, sodium or alkaline bases are required to combine with the acid bodies.

3. *Neutralization.*—This may be effected by: (a) The fixed bases of the food or by (b) ammonia. Most of the ammonia of the urine is for the purpose of neutralizing the acids. It will thus be seen that a fixed base, such as sodium is

required to carry the CO_2 to the lungs and also to enable the kidneys to excrete acids. Failing the fixed basis, oxygen is carried to the tissues, but the CO_2 cannot be carried to the lungs, hence the dyspnea of toxemia.

Another result of the effect of vitiated posterior lobe function is the loss of the glycogenic property of the liver, and a glycemia of temporary duration with frequently a glycosuria, also of temporary duration. The water-balance due to antidiuresis of the posterior lobe causes a complete upset of that fine balance of the intima of the capillaries and lymphatic channels, so that normal permeability is lost, and the increased permeability leads to a great excursion of fluid into the tissues, without a corresponding absorption of the tissue-waters into the lymphatic channels. The consequence is a general edema and water block.

The second effect of the posterior lobe overfunction is a vagotonic action, producing dilatation of all the blood channels of the abdomen, and a sympathetic constriction of all the arteries and capillaries of the body generally. This causes venous stagnation, slowing down of the heart action, and the action upon the circulation is further increased by the greater viscosity of the blood. The perivascular edema, especially about the capillaries, causes further compression of them with anemia of the brain producing a condition conducive to the cataclysm of an eclamptic seizure.

So that following upon an overplus of posterior pituitary lobe there sets in a slow insidious train of vitiated functions with an accumulation of by-products in the circulation, which, when they reach a certain stage, rapidly intensify their action by a vicious circle of production by alternating cause and effect.

Today I took the privilege of asking one of the most prominent clinical chemists in Montreal, whether it was possible for him, by all his known tests to differentiate a so-called, functional disturbance of the kidney with increased permeability, from true nephritis. His answer was enlightening—"Only in a few pronounced cases," and his rejoinder was illuminating also—"Nor can I tell how long functional disturbance may continue without producing recognizable organic disease."

Now that is the crux of the whole question of toxemias of pregnancy. How long can functional disease of the kidney persist in the chronic nephropathies without producing irreparable organic disease? In the liver we have a guide in the van den Bergh tests and clinically the advent of jaundice, but in the nephropathies we have no such danger signal; except that the high multiplication of the pressor substance in the blood in any blood pressure over 180 should be sufficient indication to warrant an interruption of the pregnancy.

From a consideration of the toxemia of pregnancy as a result of abnormal internal secretion, one can readily appreciate the profound

effect of emotions, focal abscesses, intestinal intoxications, overnutrition, and such accessory forces, which play so important a part in precipitating a crisis in mild (?) toxic cases. The pathologic changes which follow upon sepsis are so similar to those of toxemia of pregnancy, that Volhard and his school maintain that the latter is an expression of infection. One hardly need mention the influence of emotions, whether these be of long duration or of a violent nature, upon the glands of internal secretion, and I am strongly of the opinion that in this way the mental state upon entering pregnancy has a profound effect upon the course of that pregnancy. Discontent, or other emotion of an intense nature, such as fear, often starts the overproduction and initiates the vitiated function. It has always been a strong conviction with me that women who have waited long, with a strong desire for the satisfaction of their maternal desire, usually enjoy an unduly uncomplicated pregnancy. On the other hand, the disappointed, disillusioned, and unstable woman is on a fair way to trouble from the very beginning.

From the above considerations, one can see how futile treatment must be in arresting a superproduction of a compound gland substance. We can always add to a deficiency of gland secretion, but the only really effective means of abstracting a surplus from the system is by inhibiting its production by excising the gland, as in thyroidectomy. But even this palliative measure is not applicable to the pituitary. It will be seen that too much stress cannot be laid upon the early correction of any deranged function. Hence the great importance of antenatal care in the early detection of departure from the normal, thus permitting Nature to assert her own corrective power. The patient should be relieved of domestic and other worry—physical effort should be reduced to a minimum; elimination should be promoted by every means possible to free the body of the poisonous products of vitiated function; the nervous excitability should be controlled by sedatives; the blood pressure should be reduced in cases of pending or active eclampsia by blood-letting; the cause of the overstimulation of the glands of internal secretion, which is presumably the placenta, should be removed as early as is consistent with the patient's best interests. Metabolism should be reduced at first to a rate as low as possible consistent with maintenance of life, and, after improvement has set in, it should be kept as low as is consistent with maintenance of body weight. These are best accomplished by rest in bed and hospitalization if possible, seclusion as complete as possible; and in severe cases a starvation and water-free diet for three days, thereafter a carbohydrate and chloride-free diet. The bowel should be activated by colonic lavage. Sedatives, such as morphine, chloral, sodium amytal, nembutal, and veronal, should be used frequently but with discrimination, to promote sufficient mental and corporeal rest and to allay any

nervous overexcitation; by this means the patient should be reduced as nearly as possible to a vegetative stage; last, surgical intervention should step in to remove the cause:

1. In chronic cases to relieve further damage to the systems that are suffering most from the vitiated metabolism, and

2. In acute cases, to save life.

Among the chronic cases the most favorable time will usually be found to be about the third or fourth day of treatment; and in the acute cases, observation of the individual case and the experience of the obstetrician will determine whether delay and palliation are indicated, or whether active surgical intervention is imperative.

1628 Sherbrooke Street, West

COINCIDENT SURGICAL EXPOSURE AND RADIUM THERAPY IN THE TREATMENT OF EXTENSIVE CERVICAL CANCER*

Arthur H. Curtis, M.D., F.A.C.S., Chicago, Ill.

(From Passavant Memorial Hospital and the Department of Obstetrics and Gynecology, Northwestern University Medical School)

THE number of cures of cervical cancer varies roughly from 25 to 30 per cent in the major clinics of all countries, irrespective of whether the growth is removed or is treated by radium. Generally speaking, the results are very satisfactory in cancers not progressed beyond Stage I, in which cases the growth is still limited to the uterus.

In Stage II cancer of the cervix, in which the growth has progressed beyond the uterus but is still relatively limited in extent, the prognosis is dubious; in Stage III cases, with induration of the parametrium and more or less fixation of the uterus, the outlook is well-nigh hopeless. In brief, radical operation and radium treatment are relatively unsatisfactory in both Stage II and Stage III cases, and it is apparent that other procedures are required for successful management of patients with these more extensive lesions. Radical operations have evidently reached their limit of efficiency and we therefore turn now to improved radiation and allied measures for further help.

In the pioneer days of radium treatment, attempts to obtain cures with massive doses resulted in a distressingly high incidence of destructive lesions of the adjacent viscera, often terminating in fistula formation or death. We learned relatively early that the pelvic viscera are highly susceptible to injury from radium burns and, particularly, that

*Read at the Fifty-eighth Annual Meeting of the American Gynecological Society, Washington, D. C., May 8, 1933.

many cancers cannot be cured because proximity of the bladder inhibits efficient radiation. With this in mind, I have for several years made a practice of separation and upward displacement of the bladder to permit more extensive use of radium in this region without introducing the danger of vesical fistula. The additional area thus made available for radiation has permitted intensive treatment of several cases of cervical cancer which could not otherwise have been satisfactorily radiated.

The value of dissection and retraction not only of the bladder but also of the other vulnerable tissues has become more and more apparent and has eventuated in a combined method of surgical exposure and coincident radium application. The suggestions advanced in this paper pertain particularly to treatment of the Stage II group of cases and to the less advanced cases of the Stage III group in which there is some hope of cure.

PROCEDURE

The necrotic cervical growth is treated with surgical diathermy or prophylactic radiation at least three weeks prior to operation. Preliminary deep x-ray therapy may serve equally well in healing the sloughing cancerous surface.

When the surface has become free from necrosis and infection a pelvic examination is made under anesthesia to determine the extent of the growth and the amount of intervention required, and surgical exposure of the cancer-bearing uterus and adjacent cellular tissues is undertaken. With blunt dissection the bladder is mobilized upward, the cervix encircled with an incision as in making a radical vaginal hysterectomy, and the vaginal mucosa is painstakingly dissected laterally and posteriorly, along natural lines of cleavage. The body of the uterus and the regions of the broad ligaments and cardinal ligaments are now well visualized. With the organ half delivered broadside, vaginally, the bladder safely anchored in its elevated position with a catgut suture holding it high on the uterus, and the paracervical tissue exposed, a massive radium treatment is possible. Radium needles or radon seeds are now inserted where needed, near to or into the cervix or far from it, as indicated, with assurance of safety of the adjacent vulnerable organs. Although the ureters are subject to possible injury, they are considerably retracted incident to the dissection and displacement of the bladder and are relatively immune. Preliminary ureteral catheterization may merit consideration in selected cases, but we have not resorted to it. Injury of a uterine artery is a possibility; I have not yet seen that complication despite many years' custom of introducing radium needles into the cervical parametrium. Palpation of the artery preliminary to burying a radium needle in its vicinity appears unnecessary.

After burying the radium needles (or radon) as described a chain tandem of radium capsules is inserted into the uterine canal in the usual manner. A vaginal pack completes the procedure.

Until further experience warrants, the total radiation should not exceed 3,500 millicuries. Even that amount may be excessive.

REPORT OF CASES

CASE 1.—Admitted to Passavant Memorial Hospital, January 9, 1933.

History.—A married woman of fifty-eight years with two healthy children. Menopause at thirty-nine years of age; slight spotting of blood nineteen years later, in September, 1932. Rather free bleeding on one or two occasions thereafter. No pain.

Examination.—General condition good; heart and lungs normal, blood pressure 130/88, red blood count 4,720,000, hemoglobin 75 per cent, Wassermann negative. Vaginal examination revealed some urethrocele with incontinence, a relaxed perineum with slight rectocele, and a long, narrow, funnel-shaped vagina. The cervix, high up in the vaginal vault, nearly four inches from the vulva, presented a friable new-growth involving both lips. The cancerous tissue bled freely on manipulation. The wide extent of the growth in the cervix suggested some invasion of the parametrium. The uterus had limited mobility, but there was no definitely demonstrable invasion of the broad ligaments.

Surgical Diathermy Treatment.—On January 10, under nitrous oxide anesthesia, delivery of the cervix to the vulva was accomplished despite the markedly elevated position and limited mobility of the uterus. Extension of the growth was in close proximity to the bladder but the latter could be separated and was mobilized and advanced 1½ inches higher on the uterus. A moderate treatment with surgical diathermy was administered to destroy the necrotic local growth.

Microscopic study revealed a richly cellular cancer containing many epithelial pearls and cells of varied size provided with abundant mitotic figures.

On February 16, the patient was reexamined, this time under ethylene anesthesia. There was found gross evidence of remaining malignancy of the anterior lip extending rather deeply into the cervical canal and laterally somewhat into the left broad ligament. The sloughing surface of the tumor was well healed.

Surgical Procedure and Radiation.—The bladder, which had returned to its normal position since the diathermy treatment, was readily mobilized and displaced upward. A circular incision around the cervix and blunt dissection of the vagina along natural lines of cleavage exposed freely the pillars of the bladder anteriorly, the broad ligaments and cellular tissues anterolaterally, and the pillars of the rectum posteriorly. The bladder was now sutured to the body of the uterus in its reflected position in order to keep it out of the way during radiation. Seven radium needles were inserted about the cervix, chiefly laterally into the bases of the broad ligaments. Seventy-five milligrams of radium in capsules, in tandem, were placed in the uterine canal. All told, a dosage of 3000 mg. hours was given.

Postoperative Course.—The patient made an uneventful convalescence and left the hospital in a week. A notation on reexamination, April 30, 1933, reads as follows: "The cervix appears to be entirely healed and is freely movable. There is no evidence of remaining displacement of the bladder or of the reflected vaginal walls, no pelvic induration, nodulation, or tenderness. The patient feels fine, has no vaginal discharge, no urinary or bowel symptoms, is gaining weight, has a splendid appetite, and seems to be well on the way to a clinical cure."

CASE 2.—Admitted to Passavant Memorial Hospital, December 15, 1932.

History.—A married woman forty-six years old, formerly a graduate nurse. One pregnancy at the age of eighteen, terminated by spontaneous abortion in the fifth month. Menstruation was always regular, of the twenty-eight-day type, duration five days, until the menopause one year ago, at the age of forty-five. Malaise and slight pelvic distress led the patient to insert a finger into the vagina four months prior to entrance into the hospital. She felt a mass but did nothing further until three weeks prior to entrance, at which time she palpated a nodulation "like a cauliflower." A dirty, blood-tinged discharge now appeared and persisted, with increasing bloody flow as time progressed.

Physical examination revealed the patient to be in fairly good general condition; heart and lungs negative, blood pressure 130/80, red blood count 4,160,000, leucocytes 11,300, hemoglobin 70 per cent, Wassermann negative. The pelvic findings are included in the detail of the operations, recorded below.

Surgical Diathermy Treatment.—On December 17, under nitrous oxide anesthesia, the cervix was found to be enlarged to double normal size by a cauliflower-like necrotic tumor which involved the entire vaginal portion of the cervix and slightly invaded the vaginal wall in all directions. It was recorded that submucosal extension was apparently still more widespread than the surface growth and infiltration anteriorly had apparently progressed to the floor of the bladder, if not into it. "The generous sized uterus is freely movable although there must be some broad ligament invasion."

With painstaking delivery, the cervix was brought beyond the level of the vulva. Tissue was removed for biopsy. Extensive surgical diathermy was given, moist gauze packing being employed to protect the adjacent tissues.

Histologic study of the growth revealed an anaplastic epithelial cell carcinoma of the cervix.

Surgical Procedure and Radiation.—January 17, 1933, ethylene anesthesia. The diathermy treatment of a month previous, together with changes wrought by the cancerous growth, had resulted in complete destruction of the anterior cervix and a major portion of the posterior part. Slight dissection revealed the bladder lying on the uterine canal with almost no intervening tissue. The uterus was mobile. Extension of the growth anteriorly apparently had not involved the bladder, but it was much distorted and its separation and upward displacement without injury was accomplished only with difficult, painstaking dissection. Lateral and posterior dissection of the vagina was followed by further tedious complete separation of the bladder from the uterus, including opening of the anterior culdesac. An excellent delivery of an apparently hopelessly entangled and distorted uterus was obtained. This organ, which remained shrunken, was only two inches in length. Some fibrosis and residual infiltration (apparently cancerous) persisted in the parauterine cellular tissues, but evidently not beyond access of radiation, now that the dissection had delivered the uterus and had displaced the vulnerable bladder and ureters. A palisade of 8 radium needles was inserted into the tissues around the cervix and into it and one 50 mg. tube of radium was placed in the uterine canal. A total of 3,000 millicures was administered.

Rectovaginal examination, two and two-thirds months subsequently, April 5, 1933, revealed healing far progressed. The region of the uterus and its vicinity, which had been raw and necrotic during the interval following the operation, was now almost healed. The retracted tissues (still somewhat retracted a month earlier) now covered the stump nicely. The mobility of the uterus remained limited but the outlook appeared encouraging.

CASE 3.—Admitted to Passavant Memorial Hospital, November 2, 1931.

History.—A woman of forty-two years, previously married, divorced for ten years. One birth, with normal delivery at the age of twenty-one. Menstruation always regular, twenty-eight-day type, duration four to six days, normal painless flow until present trouble. Routine examination by a physician three months before hospitalization revealed a raw, ulcerated area on the cervix. No improvement with local treatments. Flowed persistently following regular period one month prior to entrance and thereafter bled rather freely, alternating with periods of spottnig until time of entrance.

Physical examination revealed a rather pale, fairly well-nourished, somewhat nervous patient. Heart and lungs negative, blood pressure 116/66, red blood cells 3,810,000, leucocytes 8,550, hemoglobin 75 per cent.

Examination and Palliative Radium Treatment.—November 3, ethylene anesthesia. Although superficially limited, the friable, bleeding lesion near the external os of the cervix was found to be an extensive endocervical cancer, apparently originating within the cervical canal. The fundus was of generous size, retrodisplaced, mobile. Gentle removal of the endocervical cancerous débris left a cavity half the diameter of the cervix, beyond which the growth had apparently extended into the left parametrium. The prognosis appeared unfavorable. A palliative intrauterine treatment with radium capsules was given.

Microscopic examination revealed a loose fibrous stroma containing islands of a squamous cell, Group 3, "middle ripe" growth.

On January 26, 1932, the patient was again given ethylene anesthesia. The fundus of the uterus was found to be large and mobile. There was a palpable thickening anterolaterally, on the left. The cervix was craterous, and the lower uterine segment slightly obstructed. Dilatation yielded some retained serohemorrhagic fluid.

The bladder was separated from the cervix, displaced upward and anchored with one catgut suture. Eight radium needles were buried in a palisade encircling the cervix and 75 mg. of radium in 2 capsules in tandem were placed in the canal. A total radiation of 1,750 millieuries was given.

Surgical Exposure and Radium Treatment.—The patient was kept under observation, with bimanual rectovaginal examination at monthly intervals. Her isolated social status and the need of a complete understanding of her condition because of her dependent child led to a frank discussion of the prognosis. The clinical course continued excellent but there remained an infiltration in the left parametrium. After prolonged temporizing, it was finally decided that radical intervention was preferable to expectancy; this, despite the fact that increasing infiltration could not be determined with certainty.

Operation, February 14, 1933, ethylene anesthesia. As a result of the previous radium treatments, the uterus presented the appearance of a clinical cure. The external os was sealed, and the canal 2¼ inches in depth, the size of the uterus was normal. The bladder was flush with the cervix and there was considerable edema in the region of the pillars. There was moderate uterine mobility, with some palpable "fullness" in the left parametrium.

The bladder was separated and displaced upward 2 inches. A circular incision around the cervix was followed by separation of the vaginal mucosa posteriorly and laterally, exposing the broad ligaments thoroughly and extending upward posteriorly to the pillars of the rectum. With the uterus thus mobilized and the bladder held up by a fixation suture, 7 radium needles were thrust into the left broad ligament, and high into the cervix anteriorly and less high posteriorly and laterally, all under digital control of the left hand, with the forefinger in the vagina and the mid-

finger in the rectum to protect against bowel injury. Seventy-five milligrams of radium in 2 capsules were placed in the uterine canal. A total radiation of 2,075 millicuries was given.

Postoperative Course.—The patient left the hospital after a week of discomfort There was no palpable exudate.

A month later, the uterus was somewhat descended, heavy, "lumpy," raw, discharging, and apparently still uncovered by mucosa (speculum examination was avoided because of excruciating tenderness).

Very recently, two months after operation and radiation, the patient returned to the hospital because of pelvic distress. Speculum examination revealed considerable necrosis of the cervical portion of the uterus and some of the adjacent parametrium. There was a rather free serous discharge containing fragments of débris. The bladder and ureters, apparently in excellent condition, had returned to normal position. The lateral vaginal walls were no longer retracted. Rectovaginal examination indicated a normal bowel and revealed no pelvic exudate, but some brawny fixation, and the patient experienced discomfort in the region of the rectosigmoid. Despite the rather extensive tissue destruction, which was more than anticipated or desired, it appeared that the process was subsiding without serious complication.

COMMENT

In view of the fact that these three patients have been cared for within the last several months, it is evident that a prognosis as to the ultimate outcome is unwarranted. Yet the fact that intensive radiation can be accomplished without injury to important structures must lead to a more encouraging outlook in cases of this character.

Complete surgical recovery has occurred in one of these cases, with accompanying gross disappearance of the growth and free mobility of a now apparently healthy uterus. The second patient has made an almost complete surgical recovery, except for some irregularity in the contour of the uterus incident to partial destruction of the cervix and lower uterine segment. The third patient has, at the present time, some necrosis of the cervix and adjacent cellular tissues with considerable associated pelvic cellulitis and profuse discharge which contains some fragments of tissue. The bladder and ureters are in excellent condition despite the nearby destructive process; this bladder would undoubtedly have been injured by the radiation had it not been spared by preliminary dissection and retraction at the time of treatment.

The raw surfaces created by the dissection in these cases apparently need cause no concern. The dissected tissues gradually fall back into their normal positions after removal of the radium. The use of sutures is unnecessary. Even the bladder reflection, despite the anchoring suture of catgut which holds it in upward displacement during radiation, quickly resumes its natural position.

Further experience may require modification in the detail of the procedure. We are most concerned with the value of the underlying principles involved.

It has been thought by many that implantation of radon seeds into the cancer-bearing pelvic tissues at the time of abdominal operation may prove to be a decided asset in our fight against cancer. Gellhorn has made intraabdominal implantations of radon under guidance of the other hand within the vagina. He then closes the abdomen and makes the usual vaginal introduction of radium. Perhaps intraabdominal placement of radon may be advantageously employed in conjunction with the procedure herewith suggested.

CONCLUSIONS

1. The feasibility of coincident surgical exposure and radium therapy in the treatment of extensive cervical cancer has been demonstrated in three cases.

2. It is my belief that acceptance of the principle of combined vaginal approach and appropriate radium therapy will result in an improved prognosis in many relatively extensive cases of carcinoma of the cervix which have heretofore had a dubious outlook.

104 South Michigan Avenue

A SURVEY OF A SERIES OF MYOMECTOMIES, WITH A FOLLOW-UP*

Hilliard E. Miller, M.D., F.A.C.S., and Curtis H. Tyrone, M.D., F.A.C.S., New Orleans, La.

(From the Departments of Gynecology of Tulane University and Touro Infirmary)

OUR purpose in presenting a survey of a series of myomectomies is to stimulate interest in an operative procedure which has a wider field of usefulness than is ordinarily recognized, and to justify its adoption as the operation of choice in a large group of cases where conservatism is of cardinal importance. Too frequently today we are asked to restore to physical health and psychical balance a young woman who has not only become maladjusted to life's problems, but permanently sterilized by an ill-chosen radical operation for the cure of fibroids. Conservatism in gynecology is a most excellent feature of our modern work, and the results of our attempts to preserve function are sufficiently outstanding to justify great pride.

The judicious selection of cases, the control of sepsis, and the elimination of hemorrhage, have not only contributed largely toward making myomectomy a relatively safe operative procedure, but have insured the restoration of a normally functioning uterus, a symptomatic cure, and the possibility of future pregnancies.

*Read at the Fifty-eighth Annual Meeting of the American Gynecological Society, Washington, D. C., May 8, 1933.

This study comprises a group of 128 myomectomies which have been done during the past eleven years on the private services of Drs. C. Jeff Miller, Hilliard E. Miller and Curtis H. Tyrone, and represents approximately 10 per cent of the total number of fibroids treated within this same period. We have been able to make specific notations in individual cases, or to follow up by letter, 94 cases, or 80 per cent of the entire group. In following up the history of these patients after operation, our endeavor has been, as far as possible, to determine to just what extent the operation has been of value in the several respects which shall be specified.

Menorrhagia, as a symptom previous to operation, occurred in 57 cases, or approximately 63 per cent. Ninety-one per cent of this group giving a history of excessive menstruation report that the duration, character and amount of flow has been perfectly normal since operation. Some few patients reported that two to three months elapsed after operation before their menstruation returned to what was considered normal so far as duration and amount of blood loss was concerned. This might be considered quite remarkable, in view of the redundant uterine tissue present after operation, and the consequent degree of involution which was necessary before the uterus would resume normal proportions. In some instances, a uterus appearing very much distorted and the size of a four months' pregnancy after all growths were enucleated, returned to a normal size and healthy tone within six weeks' time. The remaining 9 per cent of the group are patients who have reached an age where the atrophic changes in the ovaries and uterus incident to the menopause are responsible for a return of menorrhagia and other vague discomforts.

Dysmenorrhea, varying in character from mild cramps to pain severe enough to warrant narcotics, occurred in 52 per cent of the cases. Our observation has been that a fair number of women suffering from dysmenorrhea and menorrhagia in early life eventually develop fibroids. A mechanical or functional factor undoubtedly plays a very important rôle, as only 0.52 per cent of the cases reported that dysmenorrhea persisted after operation.

Postoperative pain, or pelvic discomfort of any nature subsequent to operation, was noticeably absent in the follow-up series, the great majority reporting not only that their local discomfort had been relieved, but that there had been a marked improvement in general health. Only one patient complained that a great deal of pain had followed myomectomy. Two years later the explanation of her suffering was found in a partial obstruction of the bowel, resulting from adhesions of the ileum to former myomectomy scars on the uterus.

Curettement should be a routine procedure prior to myomectomy, to avoid the likelihood of overlooking submucous fibroids, and to insure a

complete microscopic survey of the endometrium. Hyperplasia of the endometrium was reported by the pathologist in only 48 per cent of the cases; clinically the incidence was thought to be higher, but this was not borne out by microscopic examination. So far as our records show, 3 of the 8 cases which were later treated for recurrence of growths, or subsequent menorrhagia, had had a return of hyperplasia.

The number of fibroids removed at operation varied from one large subperitoneal, or interstitial type, to fifteen growths representing all types. At each end of the scale the size of the growths removed was from ½ cm. to 26 cm. in diameter. One should not be influenced by the size and position of a single fibroid in making a decision in favor of hysterectomy instead of myomectomy. It is possible in practically all cases to enucleate a single growth, even though it involves a large portion of the corpus uteri, or actually protrudes into the uterine cavity, and to restore the uterus to a normally functioning organ. The number of fibroids present will occasionally influence the type of surgical procedure: a hysterectomy is surely preferable where the number and position of the growths necessitate multiple, extensive incisions, and where marked mutilation of the musculature results from enucleating the growths. In many instances several tumors may be extracted through a single incision, and a situation which at first might appear to demand a radical approach may be converted into a relatively simple and conservative procedure. Sometimes, however, when extensive damage may result from an attempt to remove several growths through one incision, hysterectomy may become necessary.

Degenerative changes had an incidence of 32 per cent in our series, and various gradations of retrogression such as hyaline, granular, cystic, red and calcareous changes were manifested in about equal ratios. In 3 cases the pathologist reported early sarcomatous degeneration in the fibroid removed, and advised careful surveillance. In the 3 instances the patients have been under observation for three years or more, with negative clinical findings for malignancy, and one has since borne a full-term baby. Degenerative changes which have been encountered in the group were a result, as is the case in most fibroids, of either mild circulatory embarrassment, or an acute retrograde process following infarction. Such conditions should in no wise militate against undertaking a myomectomy, and will only rarely increase the technical problems by making it difficult to define the capsule. We do not recall having encountered a case where the fibroid was actually infected, or where abscess formation had occurred, except where associated adnexal infections were present. H. Lieth Murray states that in only one instance has he seen infection present in the substance of a fibroid, and that should he actually rupture an abscess in the act of performing a myomectomy, it would not deter him from completing the operation as

planned, inasmuch as he would feel certain that the patient had established an immunity to the type of organism present because of its chronicity. It would seem from the foregoing that it is not only feasible, but entirely safe, to treat fibroids conservatively by enucleation, even where extensive degeneration is evident.

In estimating the incidence of pregnancy which has followed myomectomy, we have set the age of thirty-eight as an arbitrary age limit after which conception is not likely to occur. On this premise, 69 of the 94 cases followed were possible candidates for pregnancy. The remaining 25, over thirty-eight years of age, were (1) cases where myomectomy was done in the course of other operative procedures, (2) where one large fibroid was found in an otherwise healthy pelvis, and myomectomy appeared safer than hysterectomy, and (3) a fair number of this group seriously objected to the removal of the uterus, and frankly expressed a preference for conservatism, even though subsequent treatment might be necessary in case of recurrence of the fibroid growth.

Of the 69 patients under thirty-eight years of age, 41 cases were sterile at the time of operation, and the remaining 28 had previously given birth to from one to three babies. In the 69 cases where pregnancy was a possibility, there occurred 21 pregnancies which could be considered as resulting from myomectomy, or 33⅓ per cent. Six other babies have been born to 3 of this list at subsequent dates. This gives a total of 27 babies which have been born to the 69 mothers who were considered likely to conceive after myomectomy. Such a percentage is a strong argument for conservatism in the treatment of fibroids occurring in women under forty years of age. Particularly is this true where so many factors prevail which might influence the chances of conception. Several of these patients frankly stated that they did not desire children.

The total number of myomectomies done during pregnancy was 7, a relatively small number as compared with those done on nonpregnant women. This small figure is explained by two factors. The first factor is that a very small percentage of women who have fibroids conceive. Stacy states that statistics show that only 2.6 per cent pregnancies occur where fibroids are present. While we have no figures to refute such a statement, our impression is that this figure is extremely low. The second factor is that our policy has been to treat fibroids complicating pregnancy expectantly. The great majority of these cases will proceed normally to term and deliver without particular difficulty. Not infrequently a growth which almost completely fills the true pelvic canal in the early months of pregnancy, is dislodged and carried well up into the abdomen, where its size and position have no influence on the mechanics of delivery. Cesarean section and myomectomy, or a Porro operation, depending upon which is indicated, is preferable for those cases at term where the birth canal is obstructed by growths.

Myomectomy during the course of pregnancy has only been resorted to when an acute abdominal condition has arisen from degeneration in a growth due to strangulation of circulation, from emboli, or twisting of the pedicle. The technical difficulties are increased many times where myomectomy is necessary during pregnancy, particularly if the growth, or growths, are situated near or over the placental implantation. Many and huge venous sinuses are opened in this area when a fibroid is enucleated, resulting in profuse hemorrhage, which will tax the speed and ingenuity of the operator. Indeed, we recall a case where great risk was incurred by apparently unavailing attempts to check the hemorrhage which resulted from the removal of a fibroid with a sessile base from a pregnant uterus. Only after applying great quantities of suture material, inserted in various ways, supplemented later by transfusion, was the patient restored to a satisfactory postoperative condition.

Our success, so far as continuance of pregnancy is concerned, is quite in accord with other reports. In our series 5 out of 7 cases, or approximately 71 per cent, continued to full-term pregnancy after myomectomy. While this series is too small to warrant drawing any conclusions, the formidable nature of the operation, and unsatisfactory prognosis for the fetus, should deter us from making too hasty a decision to operate. Many apparent acute cases may be tided over the acute stage by the administration of frequent and large doses of morphine, and permitted to go to term without operation. This is particularly true where signs of toxemia are absent which would indicate a necrobiotic process. Giving the operation credit for inducing miscarriages in all cases is possibly unwarranted, as undoubtedly the pathologic process in many instances is of such grave nature as to have rendered the emptying of the uterus inevitable.

The subsequent obstetric histories of our patients who have been subjected to myomectomy have been the same as those observed by other investigators. So far as can be determined from letters from patients who were not confined in our service, and from what was observed in the cases supervised by us, there has been no increase in malpositions of the fetus, nor has there been any more dystocia than would be expected to occur as a consequence of the age of the patient. Cesarean section was done in one case in our series. In this case a patient, aged thirty-eight, who was two months pregnant at the time, was found to have a fibroid not only undergoing acute degeneration, but so large that it was impacted in and completely filled the pelvis. At operation the growth, largely intramural in type, was removed from the posterior uterine wall. The size of the growth, and the extent of involved uterine musculature, necessitated an incision extending throughout the length of the pregnant uterus, and when the growth was extracted the decidual

lining of the uterus was exposed. The patient had a normal convalescence from the operation, and while considerable apprehension was felt for the safety of her pregnancy, her progress to term was uneventful. At the onset of labor, the membranes ruptured and on examination the cervix was found to be long and hard, and the baby, which was large, was presenting as a breech. These factors, plus a recent extensive scar in the uterus, and the patient's great desire for a baby, prompted the selection of cesarean section as the safest method of delivery. Inspection of the myomectomy scar was made at the time and much to our gratification it gave no evidence of weakness, nor did the uterus seem to have been disturbed in its uniform expansion to accommodate the growth of the baby. This patient three years later had a second section. The literature reveals only the very occasional case of rupture of the myomectomy scar during labor, and most writers who have had the opportunity of inspecting the scar at a subsequent operation, expressed the belief that the tensile character of the scar compared favorably with that of healthy musculature.

The number of patients who returned after myomectomy for treatment was 8, or approximately 8.5 per cent of the 94 followed. Of this number 5 were found to have had a recurrence of menorrhagia resulting from generalized sclerosis of the uterine musculature. Hysterectomy was done for 3, and radium used for 5 of these return group cases, to relieve them of their symptoms. A time interval of from three to ten years existed between the date of myomectomy and the return of symptoms which necessitated treatment in this group. The youngest to return was thirty-eight, a patient who had had a myomectomy three years previously without relief from menorrhagia. This symptom was controlled subsequently by a short application of radium. The remaining 7 of this group had advanced in age to or beyond the menopausal phase before return of symptoms occurred, the youngest being forty-five and the oldest fifty-one.

There was one death in the entire series of 128 cases, giving an operative mortality of 0.77 per cent. This one patient represents the only patient who died from any cause during the hospital stay, and death in this instance was due to acute dilatation of the stomach. The low mortality percentage argues very favorably for the safety of myomectomy as compared with hysterectomy; indeed, in our series of cases the mortality is less than one-half of that encountered in hysterectomy.

The immediate and remote postoperative complications following myomectomy in our cases were of a very serious nature, and no doubt resulted from some faulty operative technic, such as slough of the uterine muscle resulting from tying sutures too tight, or inability to completely cover all raw surfaces. Two cases developed acute intestinal obstruction during their stay in the hospital, both recovered after release of the

adhesions which had formed between a loop of the ileum and the myomectomy scar, and draining the small bowel through a catheter inserted into the ileum above the point obstructed. A third patient was eight months pregnant, following a myomectomy sixteen months previously, when the bowel became obstructed. At operation a loop of ileum was found to be obstructed by organized bands of adhesions attached to the scar on the posterior uterine wall. This patient recovered and delivered a premature baby two days after operation. A fourth patient reported in the follow-up study that she had been operated upon subsequently for chronic partial obstruction of the bowel.

SUMMARY

1. Myomectomy is a safe and conservative treatment for fibroids, as represented by a mortality of 0.77 per cent in 128 cases.

2. This procedure offers almost complete relief from dysmenorrhea and menorrhagia which result from the presence of fibroids.

3. The reasonable expectancy of pregnancy in young women under thirty-eight years of age, following myomectomy, according to our series is 33⅓ per cent.

4. The percentage of recurrence of fibroids after myomectomy was 3.08 per cent in our experience.

5. Myomectomy during pregnancy is only indicated where definite necrobiotic processes are present.

6. In the series analyzed, acute obstruction of the bowel occurred in 1.5 per cent of the patients during the hospital stay; 0.75 per cent acute obstruction occurred subsequently as a complication of pregnancy, and 0.75 per cent chronic partial obstruction.

209 Medical Arts Building

ENDOMETRIAL HYPERPLASIA AND ITS RELATION TO ENDOCRINE DYSFUNCTION*

JAMES E. KING, M.D., BUFFALO, N. Y.

THE clinical importance of endometrial hyperplasia and the frequency with which it occurs justified the efforts during the past few years, to determine its cause and understand its significance. The older textbooks regarded the condition as a hypertrophy of the endometrium and explained its occurrence as the result of passive congestion. The pathologists soon established its true position as a hyperplasia and a new interest was awakened. Inflammation and congestion as the etiologic factors were then discarded, and a number of theories based upon an endocrine cause were suggested. The work of Hitschmann and Adler added support to these endocrine theories. However, the lack of exact knowledge concerning the source and part played by the various endocrine factors responsible for the normal endometrial changes, naturally precluded any wholly satisfactory explanation to account for abnormal reactions. The next advance was the demonstration of the complex interrelation between the pituitary and ovary upon whose orderly functioning, together with the temporary glandular structures, the phenomena of normal menstruation was shown to depend. While much knowledge has been forthcoming regarding these glandular relationships, there is still confusion abroad and certain questions remain to be satisfactorily answered before the real sequence of events involved in menstruation is definitely and finally known. It is, therefore, not surprising that the search for the causes and significance of hyperplasia is still in a state of flux. This being the case, it might be profitable to review the subject, as it now stands, in order that our position relative to its pathology, etiology, and treatment may be defined.

Of fundamental importance to any discussion of the subject of hyperplasia is a consideration of its gross and histologic features and the criteria upon which its histologic diagnosis rests. Fortunately here, there is slight ground for dispute, for the cellular pathology has been well established by foreign and American pathologists. The gross picture is a familiar one. The endometrium is in whole or in part thickened to various degrees and is often seen in folds or with the development of polypoid formations. Histologically, all the layers of the endometrium undergo hyperplasia. The most striking and characteristic finding is the increase in the number and size of the glands which often show cyst-like dilatations. The stroma cells are definitely increased and are

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frequently seen in spindle shapes. In some locations these cells will be closely packed, while in others there will be areas of distinct edema. Mitotic cells are usually found. Although most of the epithelial cells retain their high columnar type, those lining the dilatations may become low cuboidal, probably as the result of pressure. The vessels are increased in number, are prominent, and often show thickened walls. While the above may be considered to be the essential characteristics of a true hyperplasia, certain writers have stressed less constant features, such as thrombosis, intraglandular papillary outgrowths, areas of surface necrosis, and small hemorrhages into the substance. These findings should be regarded as incidental and not of fundamental importance.

Long before any of the specific hormones of the ovary were definitely known, the view that hyperplasia was the result of an endocrine influence prompted the study of the ovaries in connection with such cases. Recently Novak and Graves have studied a series of cases and their observations are in general accord with those of others who earlier attempted to show such a relationship. All have described ovaries that contain follicle cysts, and Graves believed that the fluid of such cysts was rich in folliculin. In many of these cystic ovaries no corpus luteum was seen, while in others it was degenerated or defective. Schroeder expressed the belief that hyperplasia was due to the continuous secretion of these follicles which was possible through lack of the influence of the normal corpus luteum. Despite the fact that Novak and Martzloff found corpora lutea in some cases of hyperplasia, it may be definitely accepted that the distinctive ovarian findings are the numerous cystic follicles and, in the majority of instances, the absence of the normal corpus luteum.

However, as cystic ovaries are so common and so frequently seen in women showing no abnormal bleeding, it would appear that the more important feature must be considered to be the absence of a normal corpus luteum. Notwithstanding these constant ovarian findings, any attempt to correlate them with the presence of hyperplasia must be largely on theoretical grounds. This possible etiologic relationship between the ovaries and hyperplasia has suggested a terminology to indicate the ovarian influence. Brennecke in 1882 suggested "hyperplastic endometritis ovarialis." Harte, also believing the condition to be due to continued and excessive ovarian stimulus, characterized it as "subinvolution deciduae menstrualis." It has now become evident, however, that a terminology indicating an ovarian influence alone was premature.

The attempt to determine the cause of hyperplasia has led to much animal experimentation, and certain theories have been based upon the results. Reasonable theoretical explanations to account for disease conditions are of distinct value. They furnish a base line for experimentation and reasoning, and many a theory of yesterday has become knowledge of today. It is therefore proper that the theories proposed,

especially those based upon experimentation, be given due consideration and be received as distinct contributions to this subject.

The older views, before any real facts of the ovarian hormones were known, have been already touched upon. After the follicle hormone and the important rôle of the corpus luteum were demonstrated, there were grounds for more elaborate theories based upon a more specific reasoning. It is unnecessary to review here the painstaking work of the many investigators who have contributed so much to present-day knowledge of the reproductive cycle. Their work has directly or indirectly been a distinct contribution to the subject of hyperplasia. Efforts to establish the various hormones of the ovary as factors in hyperplasia, are at the present moment, however, confusing and inconclusive. The view that failure of the corpus luteum is responsible, as elaborated by Schroeder, has found support from Shaw, Novak, and Graves who believe that deficiency or absence of corpus luteum hormones permit an excess of estrin which is responsible for the progressive increase of endometrial tissue. Burch produced comparable changes in the endometrium of mice by injection of estrin, thus apparently establishing experimental ground for these views. Here, then, we have some evidence that the persistent uncontrolled follicles noted in the ovaries are directly responsible for the endometrial changes. At this point an inquiring mind asks: if such an explanation be true, what are the factors that have so disturbed the orderly ovarian function? An answer is at hand. With the positive evidence of the essential rôle assumed by the anterior pituitary as an activator and as a control of ovarian function, a field for further conjecture and experimentation in the solution of the problem was afforded.

The most outstanding experimental work bearing upon this phase of the problem are the experiments of Hofbauer published in 1931. By implantation of anterior lobe into guinea pigs, and in other instances by injection of anterior lobe extracts, changes in the endometrium comparable to those of hyperplasia were produced. Not only that but the ovaries also developed cystic follicles quite similar to those in human ovaries associated with hyperplasia. Here then again is a theory with a background of experimental proof that is not antagonistic but complemental to the theory based on ovarian dysfunction. In principle, both of these views are appealing, and their acceptance, in whole or in part, established hyperplasia not as a clinical entity but as the end-result of misdirected glandular function.

The clinical phenomena in connection with hyperplasia are well known and require no review here. It is sufficient to say that it accounts for about 50 per cent of all cases of abnormal bleeding from puberty to the menopause. The degree of hyperplasia does not always determine the amount or character of the bleeding, and Novak has even found it associated with amenorrhea. This finding of Novak has not been ob-

served by the writer, but, as Novak says, these cases may be overlooked because curettage is commonly not done in amenorrheic patients. On this point the clinician has opportunity to furnish evidence, although to establish it definitely will still further complicate the picture. Certain it is, that with the varied character of the bleeding there is at present no reliable clinical evidence upon which it is possible to base a diagnosis of hyperplasia. Clinical diagnosis is based upon presumption only. Novak made the attempt, apparently without success, to find associated indications of glandular dysfunction in order to establish, through a more complete clinical picture, an exact basis for diagnosis. It is highly probable that should any method of diagnosis be found other than the presence of the hyperplasia itself, it will be by some biologic test.

In connection with the clinical side of hyperplasia the causes underlying the bleeding are of real importance and interest. The first question as to whether the periodic flow in such cases may be regarded as true menstruation is not entirely an academic one. To the clinician "menstruation" implies a bleeding that is the result of a complex interrelationship of various endocrine secretions produced by the normal, orderly operation of the glandular structures concerned. For bleeding, therefore, that occurs through failure of these normal physiologic processes, the term *dysfunctional* bleeding is both descriptive and appropriate.

Explanation for the bleeding is still conjectural. The view that it is due entirely to an endocrine factor is supported upon theoretical grounds and more recently also by the results from the use of the anterior pituitary principle which bears prolan B. Others, believing that it is due to causes residing in the endometrium itself, point to the thrombosis with necrosis that is frequently seen. Bleeding as a result of diapedesis has been suggested, and areas of extravasated blood in the stroma are offered in evidence. The fact that curettage is often followed by cessation of bleeding, with a return to a more or less normal periodic flow, makes it difficult to convince the clinician that, in some cases at least, the endometrium itself is not responsible for the bleeding.

It might appear that, with such reasonable theoretical grounds for the support of an endocrine cause for the bleeding, and with such clinical and histologic evidence in support of a mechanical cause, the clinician should, for the present at least, accept the possibility of both explanations. By doing so he will approach the more practical side of the question with an unbiased mind, and be able to reconcile apparent contradictions in the clinical manifestations, and to appraise more judicially the results of his treatment.

Another fact of interest bearing on the clinical side of hyperplasia is its frequent association with fibroid tumors. This is a matter of common observation, but there is as yet no adequate explanation to account for it. Its frequency would surely exclude its being a chance relationship. It

is more commonly found in connection with the smaller tumors, as the larger ones by stretching and pressure are more likely to produce endometrial atrophy. In a series of 114 fibroids treated by radium, I found that 81, or 71 per cent, showed hyperplasia. The practical point in this connection is that bleeding associated with many of these tumors is undoubtedly due to the presence of hyperplasia and not primarily to the fibroid. A further suggestive fact is found in the frequent combination of endometrial and myometrial hyperplasia, and the clinician awaits with interest any forthcoming explanation.

The ultimate object of investigations into the cause and pathology of a disease is that a remedy for its relief or cure may be evolved. In the present state of our knowledge it is only natural that the suggested therapeutic procedures for the treatment of hyperplasia should be somewhat confused.

Present treatment may be divided into that directed to the pathologic condition itself and that based upon the more or less theoretical conceptions as to its cause.

In connection with the treatment of the pathologic condition itself curettage is the oldest treatment and the temporary, or occasionally permanent, relief it affords still entitles it to consideration. The tendency to recurrence necessitating repeated curettage naturally suggests hysterectomy as a certain means of cure. The further fact that women at or near the menopause are prone to develop body carcinoma when prompt return of the hyperplasia takes place, supplies in such cases, a well-grounded argument for hysterectomy. Certainly there are cases for which radical surgery is still justified. The great majority of cases, however, for which hysterectomy would formerly have been proper, may today be successfully treated by curettage and radium. Even in younger persons radium in suitable dosage is a most valuable treatment.

The earliest attempts at treatment based upon theoretical grounds were conservative operations upon the ovaries. Such procedures were soon found to be useless, as nothing short of ablation influenced the condition.

Based upon his experiments indicating the anterior pituitary as the fundamental cause of hyperplasia, Hofbauer suggested irradiating the pituitary and reported that it had proved of value in his own and in the hands of others. I have had no experience with this treatment, but it is difficult to understand a selective action of the rays for the particular group of cells concerned in the cause of hyperplasia. Even provided that there be a definite and positive reaction of the hypophysis to such irradiation, it is easily conceivable that other functional activities of the gland might be disturbed.

Novak's proposal for the use of the luteinizing principle of the anterior pituitary is a reasonable corollary to the theory that its absence and consequent failure of luteinization is responsible for the bleeding. His

discussion of its use from various angles, however, reflects his own uncertainty as to its real action in those cases in which prompt results were obtained. My experience with it has been somewhat disappointing. Even in cases which clinically conform to the so-called adolescent bleeding in which on theoretical ground its use was clearly indicated, the results obtained were in no sense uniform. The uncertain potency of the preparation may account in some instances for failures, and it is probable that when a more perfectly standardized and staple preparation is available, further clinical use will establish its place in treatment. Unfortunately, the conspicuous failures in the practical application of endocrine therapy to conditions which theoretically should respond, have engendered a skepticism that may result one day in our throwing the baby out with the bath water.

The clinician would be the last to wish to add anything to the discussion of hyperplasia and dysfunctional bleeding that might further complicate the situation as it now stands. From his clinical experience, however, it is difficult to understand how the importance of the thyroid in these conditions can be entirely ignored. Both experimental and clinical evidence clearly indicate the essential rôle of the thyroid at puberty. Additional evidence is found in periodic swelling during menstruation and in the enlargement and the not infrequent clinical evidences of thyroid dysfunction during pregnancy. The therapeutic value of thyroid in certain cases of sterility, habitual abortion, and dysfunctional bleeding at or near the menopause, bears witness to the fact that in these conditions the thyroid occasionally occupies a key position. An attempt to explain in what way its influence is exerted, opens a wide field for conjecture, and upon this point I have nothing to offer. Its relation to hyperplasia and dysfunctional bleeding would seem to indicate that until more definite knowledge is forthcoming, the clinician must regard dysfunctional bleeding as the expression of a primary dysfunction of any one of several glandular structures concerned in the menstrual cycle. With this concept he may better interpret the clinical phenomena and receive with unbiased mind suggestions for treatment.

1255 Delaware Avenue

REACTION OF THE MATURE HUMAN OVARY TO ANTUITRIN-S*

SAMUEL H. GEIST, M.D., NEW YORK, N. Y.

(From the Gynecological Service and the Department of Laboratories, Mount Sinai Hospital)

WHEN an immature female rodent is injected with urine from a pregnant woman, its ovaries react by showing a premature maturation of the follicles and a marked corpus luteum formation. It is of importance to ascertain whether the human ovary reacts to injections of the hormone as does the rodent ovary.

Zondek,[1] in three women after fourteen days of subcutaneous injections of prolan, was able to demonstrate cysts in the ovaries. He suggested a relationship between the microcystic ovaries of human beings and a disturbed pituitary action.

Fig. 1.

Fig. 2.

Fig. 1.—Ovary showing marked hemorrhage into corpus luteum. Hemorrhagic extravasation in and about large atretic follicles, hemorrhage into the stroma. Marked congestion of entire ovary.

Fig. 2.—Enlarged ovary showing numerous cystic atretic follicles with hemorrhage, and congestion of stroma and hilus suggesting a positive Aschleim-Zondek reaction.

Mandelstamm and Tschaikowsky[2] injected 10 women subcutaneously with from 400 to 1,100 mouse units of prolan. One hundred to two hundred units were injected daily. All the cases showed changes in the follicular apparatus. They found degenerating ova in the ripe follicles, desquamation and disappearance of the granulosa, cystic follicles, and many corpora lutea. There were many corpora albicantia and marked congestion and hemorrhage in the stroma.

E. J. Kraus[3] studied the ovaries in children and adults suffering from intracranial lesions associated with prepituitary hypertrophy and an excess of prolan

*Read at the Fifty-Eighth Annual Meeting of the American Gynecological Society, Washington, D. C., May 8 to 10, 1933.

in the blood. He found microcystic disease of the ovaries. The ovaries contained cysts from pea- to bean-sized, some of them with a low epithelial lining, some with the epithelium desquamating, and in some instances no epithelium was found. A few contained a cumulus with a degenerating ovum. In some cases the cysts presented an obliterative process, with corpora atretica as the end-result. There was also present a layer of fatty theca interna cells. The ovaries themselves were large and markedly congested. Corpora lutea were absent or rare.

Hisaw[4] and his coworkers have shown that in the sexually immature monkey, by means of massive subcutaneous doses supplemented by intravenous administration of an active anterior pituitary hormone derived from sheep, a luteinization of the ovary takes place comparable with the reaction in the rodent ovary.

Engle,[5] in the monkey, was able to produce an increase in atretic follicles and hyalinization, with anterior pituitary-like hormone. He was able to show that the reaction to anterior pituitary-like hormone differed from the response to the true prepituitary hormone.

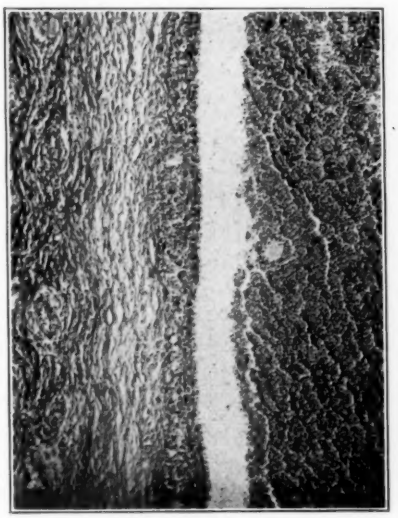

Fig. 3.

Fig. 4.

Fig. 3.—Wall of cystic atretic follicle lined with low epithelium and showing congestion and hemorrhage into and about the follicle.

Fig. 4.—Wall of cystic atretic follicle showing a lining composed of many large granulosa cells and persistence of theca interna cells separated by a definite fibrous layer. Perifollicular hemorrhage.

Selyl and Collip[6] were able to produce a luteinization of the theca interna cells in immature rats, using an anterior pituitary-like hormone. Adults reacted by ovulation and corpus luteum development.

Cushing and Davidoff[7] reported a case of acromegaly associated with a chromophilic adenoma. The ovaries in this case showed four cysts, "a large one," another with a ripe ovum, and two that were described as fully developed graffian follicles.

These observations and numerous reports of the production of similar lesions in the ovaries of various species of animals treated either with prolan or real prepituitary hormone or pituitary transplants, led us to try and produce changes in the human ovary with antuitrin-S,* a hormone obtained from the urine of pregnancy.

*We are indebted to Parke, Davis & Co., for the material used in this investigation and their interest in the problem.

In 50 cases, in women between the ages of thirty-three and forty-eight, varying doses of antuitrin-S, from six hundred rat units to twenty-two hundred rat units, given over a period varying from thirty-six hours to one hundred hours, resulted in definite changes in the ovaries. The injections were given subcutaneously, as much as six hundred units being given in one day in divided doses. In 33 cases the changes to be described were found. In a control series of 25 non-injected cases the ovaries in 4 showed changes comparable to those found in the injected cases. It is easily understood that the exhibition of active antuitrin-S might call forth a reaction that physiologically is present only at times in the ovary, though this reaction might be exaggerated beyond the normal by the injections.

Fig. 5.

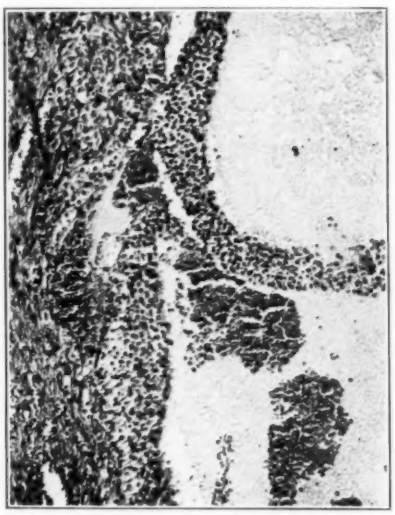

Fig. 6.

Fig. 5.—Wall of two adjacent atretic follicles showing congestion, perifollicular hemorrhage, persistence of theca lutein cells, and a lining composed of many layers of granulosa cells.

Fig. 6.—Wall of an atretic cystic follicle showing perifollicular hemorrhage with extravasations into the follicle. Desquamating granulosa cells and persistency of fatty theca cells.

The ovaries of the injected patients were obtained at operation, usually performed for uncomplicated fibroids. They presented a marked congestion of the vessels of the hilus with occasional extravasations into the hilus, probably due to rupture of small vessels or diapedesis. In the stroma, likewise, there was a marked increase in the vascularity and not infrequently hemorrhagic extravasation.

Apparently there is no stimulation of the follicle; rather an arrest of follicular development. The impression derived is that the follicles cease to develop beyond the point that they have reached at the time of the injection. The number of cystic follicles seems increased. They are from 2 to 20 mm. in diameter. The wall is smooth or thrown into

small folds; the lining is glistening or dark and pigmented. A characteristic finding about these cystic follicles is the presence of hemorrhage; in some cases this perifollicular hemorrhage has extended into the cavity of the follicle. Occasionally the gross appearance suggests the positive Aschheim-Zondek reaction in the rodent. (Figs. 1 and 2.) The lining of the cystic follicle varies. In some specimens the epithelium is low (Fig. 3), in others many layers of granulosa cells are present. (Figs. 4 and 5.) Occasionally there is no demonstrable epithelial lining. Cast off masses of granulosa cells are found in the follicular fluid and the inner wall occasionally presents a granulosa layer that is being desquamated. (Fig. 6.) In some sections ripe follicles are arrested and show a cumulus with a degenerating ovum

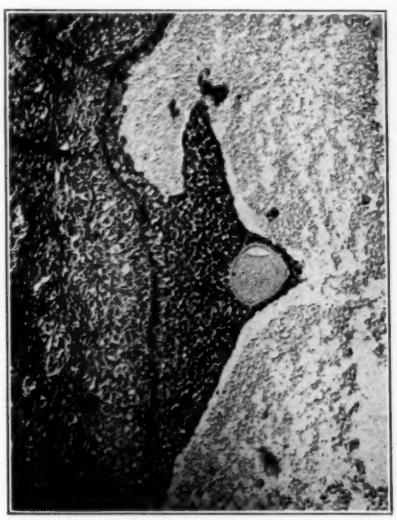

Fig. 7.

Fig. 8.

Fig. 7.—Wall of cystic atretic follicle showing a cumulus, degenerated ovum, and persistence of fatty theca lutein cells.

Fig. 8.—Wall of atretic follicle showing persistent fatty theca lutein cells in large numbers. Marked peri and intrafollicular hemorrhage.

with theca cell hypertrophy. (Fig. 7.) The theca lutein cells in many instances are prominent (Figs. 8 and 9), and increased in number. Occasionally a corpus luteum is found with massive hemorrhage into it. (Fig. 10.) The intensity of the reaction in the ovary seems to bear a direct relationship to the amount of hormone injected. The cases that were injected over a period of ninety-six hours or more seemed to be most affected.

In normal pregnancy the ovaries present changes somewhat similar to those we have just described, and it is possible that this similarity is dependent on the same factor, the increase in anterior pituitary-like hormone in the blood. Novak and Koff[8] have described similar pictures in chorioepithelioma and hydatidiform moles.

The findings that have been described suggest that the substance exhibited has a definite effect on the human ovary. However, it must be kept in mind as pointed out by Engel and others that the reaction to the anterior pituitary-like hormone and to the prepituitary hormone or pituitary transplant is not entirely similar. Nevertheless it is possible that if a better method of administration can be devised, such as the subcutaneous combined with the intravenous administration as Hisaw and Engel have carried out in the monkey, a means may be

Fig. 9.

Fig. 10.

Fig. 9.—Wall of follicle showing persistent masses of fatty theca lutein cells, remains of granulosa cells, and marked intrafollicular hemorrhage.

Fig. 10.—Corpus luteum showing marked hemorrhage into its substance, similar to pictures seen in the corpus luteum of pregnancy.

available to obtain, more consistently, changes that would influence the physiologic process in the human being and the lead to definite clinical results.

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100 EAST SEVENTY-FOURTH STREET.

A STUDY OF THE EFFECTS OF THEELIN ON GONORRHEAL VAGINITIS IN CHILDREN*

ROBERT M. LEWIS, M.D., NEW HAVEN, CONN.

(From the Department of Obstetrics and Gynecology, Yale School of Medicine)

THE treatment of gonorrheal vaginitis of childhood presents a troublesome problem that has never been satisfactorily solved. Regardless of the method employed the vaginitis frequently persists for many months or even longer unaffected by therapy. In our larger cities the disease is a serious social problem and a scourge in institutions for children.

In the child's vagina the infecting organisms lie within the interstices of the epithelial cells or in the subepithelial space. Bearing this point in mind it is evident why the usual application of antiseptics, which are unable to penetrate beneath the superficial epithelium to the habitat of the gonococcus, yields disappointing results.

The consideration of certain well recognized facts suggested the possibility of eradicating the gonorrheal vaginitis of children by the application of a radically new method of treatment. We know that the gonococcus is a highly selective organism able to exist only in certain tissues. We know also that the infection subsides before the changes of puberty have converted the delicate thin layered epithelium lining the child's vagina to the thicker structure of the adult.[1] Finally, primary infection of the adult vagina is either extremely shortlived or nonexistent.

With these facts in mind the thought occurred that, if one were able to change sufficiently the character of the epithelial lining of the child's vagina, one might reasonably hope to destroy the invading gonococcus by making its habitat unfavorable. Edgar Allen, in 1928, employing ovarian hormone, demonstrated that such a transformation could be effected in the case of the immature monkey. Could it be obtained in the child? After the injection of 1005 rat units of ovarian hormone over a period of twenty-one days Allen found that the vagina of the monkey exhibited an epithelium averaging thirty layers in thickness and differentiated into two zones. The vaginal epithelium of the control monkey, on the other hand, remained four to eight layers in thickness. Smears showed a proportional increase of partly or completely cornified epithelial cells. Associated with the vaginal changes there was some development of the cervical glands and an invasion of their lumina by many polymorphonuclear leucocytes. The endometrium was "built

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up'' at most to a midinterval phase. Involution of the structures affected by theelin occurred in a few weeks subsequent to the last injection of the hormone. The results of Allen's experiments raised the question whether corresponding changes in the vaginal epithelium could be produced in the immature human female, and, moreover, if they were produced would the gonococcal infection be thereby eliminated? It was recognized, of course, that, if the paravaginal glands were involved along with the vagina, reinfection from this source would nullify any results that might be obtained. Fortunately, owing to the lack of development of these structures, such an infection is a rarity. An endocervical infection would have the same unfortunate effect unless the leucocytic invasion invoked by theelin would simultaneously rid these structures of gonococci.

The next question which arose was, would the injections of theelin be an entirely safe procedure when administered to the child. The answer seemed to be afforded by the work of Hartman.[2] This investi-

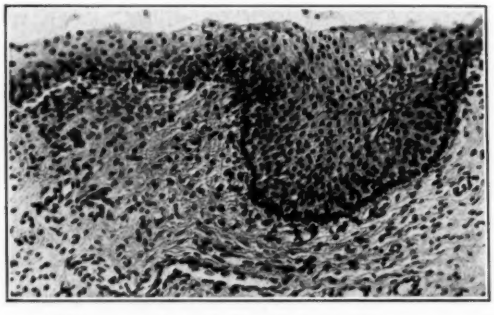

Fig. 1.—Vaginal epithelium of infant two and three-quarter months old. Autopsy specimen. In general but little change in thickness of layers is noted up to about ten years of age.

gator found that uteri of immature monkeys after treatment with theelin may bleed without showing ma roscopic change, and that the threshold of such bleeding is far below the level at which estrous changes occur in the uterus and ovaries and well above the level required to produce changes in the vaginal epithelium. Theelin administration will not develop the endometrium beyond the midinterval stage. Hartman believes that the administration of the hormone may induce a temporary inhibition of growth changes in the follicles of the ovary but that such an effect is only temporary and that no permanent damage to the ovary results. As the result of experiments with animals he is of the opinion that the dosage of theelin required to produce vaginal reaction is far less than that which would lead to injurious changes or uterine bleeding, and that theelin is so readily excreted by the kidney that no deleterious effect results from cumulative action. Accordingly it seemed safe to subject children with gonococcus vaginitis to treatment with theelin.

The treatment has been carried out on eight children suffering from severe vaginal infections accompanied by a purulent discharge. All eight patients were selected as typical cases of gonococcal vaginal infection. Throughout this study the presence of a purulent vaginal discharge and of smears showing gram-negative intracellular diplococci morphologically resembling gonococci was taken as a criterion for the diagnosis of gonococcal infection. We were unable to obtain positive cultures from the vagina in any of these cases. However, since it is difficult to cultivate the organism on laboratory media, failure to secure positive cultures does not necessarily invalidate the diagnosis. One of the children presented a typical gonococcal arthritis and positive cultures were secured from the aspirated knee joint involved. In another child, five days of age, a typical gonococcal ophthalmitis developed, which in twenty-two days was followed by vaginal infection.

In the eight children constituting this series no other form of treatment was employed while theelin was being given. The vulvar surface only was sponged with salt solution when it became fouled with vaginal secretions. Four of the patients presented themselves with recent untreated infections. The remainder gave histories of a gonorrheal vaginitis of from six to twenty months' duration. In none of these had treatment been given during the three weeks preceding the administration of theelin.

All the patients received daily either one, two, or three hypodermic injections of theelin of 50 R.U. each in the arm or the leg. In four instances (Cases 1, 5, 6, and 7) theelin was also given in small quantities by vaginal suppositories. The use of this method of administration was soon abandoned as an unnecessary adjuvant.

The total dosage of theelin, as well as the duration of its administration required to arrest all vaginal discharge and cause the gonococci to disappear from the vaginal smears varied widely. In the first four cases we adopted an ultraconservative course. In each of these patients theelin was given for ten or twelve successive days only, the total amounts varying between 850 and 1000 R.U. The child who was given 1000 R.U. hypodermically received also approximately 250 R.U. by vaginal suppositories. This group of four consisted of patients with long standing infections all of whom had been treated previously with local antiseptics.

The four patients of the second group presented recent infections. Here larger quantities of theelin given over a longer period were necessary to arrest the vaginal discharge and to yield smears negative for gonococci. In this group the patient receiving the least amount of theelin was given, over a period of nineteen days, a total of 2800 R.U. hypodermically and 450 R.U. by vaginal suppositories. The leucorrhea stopped soon after treatment was begun and smears became negative after twenty days. There was no recurrence of symptoms at the end

of the four months when the child was last examined. Another child received 100 R.U. daily for thirty-one days. The discharge ceased and smears became negative on the twenty-sixth day of treatment. The longest course of treatment continued for ninety-eight days. During this time, with occasional interruptions, 8450 R.U. of theelin were given hypodermically and 250 R.U. by vaginal suppositories.

No local irritation resulted from the administration of theelin nor were there unfavorable general symptoms. In Case 5 of the second group, after twelve days treatment, the child complained of abdominal pain and a temperature of 40° was noted. The leucocyte count rose from 10,000 to 25,000. The patient did not vomit. There was neither abdominal rigidity nor localized tenderness, although palpation of the

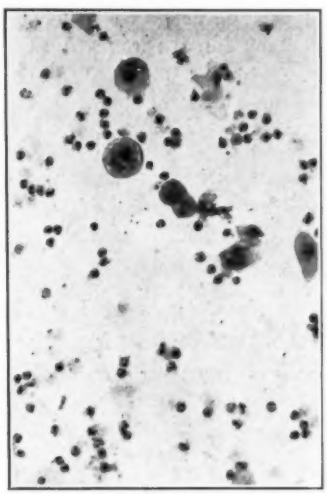

Fig. 1.

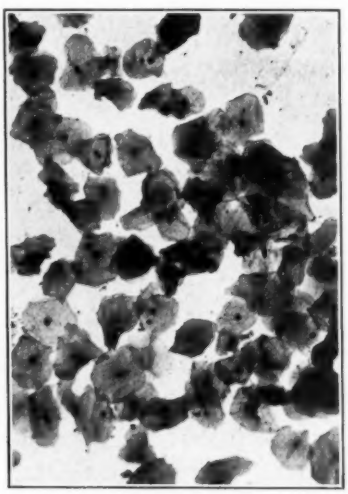

Fig. 2.

Fig. 2.—Vaginal smear before treatment with theelin.

Fig. 3.—Shows character of vaginal smear in a case seventeen days after treatment with theelin was begun. Note abundance of desquamated epithelial cells with pyenotic nuclei.

abdomen was painful. Rectal examination was negative. The throat was moderately inflamed. Fearing a possible peritoneal infection the injections of theelin were temporarily discontinued. Within twenty-four hours the temperature became normal and the pain disappeared, a sequence of events which would seem to indicate that the symptoms in question did not arise from a peritonitis. Treatment with theelin was now resumed. From a biologic standpoint it is of interest to note that this child showed a slight hypertrophy of the right breast toward the end of her rather long treatment.

The children receiving the larger amounts of theelin exhibited an hypertrophy and increased vascularity of the labia majora and minora and of the introitus which resembled the conditions found in the new-

born child. In no case did uterine bleeding result from or follow the treatment with theelin.

During hospitalization of the patients vaginal smears stained by Gram's method were examined in some instances daily, in others every three or four days. In the majority of the cases vaginal discharge ceased in one to three weeks after treatment was instituted. At the conclusion of treatment the discharge was absent in all eight cases and smears were negative for gonococci. Desquamation of epithelial cells in large numbers was usually found in seven to twenty-one days. In several instances this desquamation was so great that cheesy or scaly plugs were extruded from the vagina. Microscopically, as shown in Fig. 3, the plugs consisted of large polygonal epithelial cells.

Fig. 4.

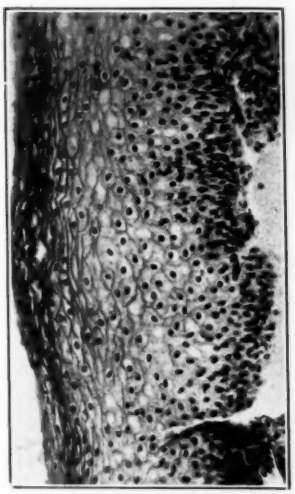

Fig. 5.

Fig. 4.—Vaginal epithelium (biopsy). Case 6 before administration of theelin. Note the leucocytes between the epithelial cells.

Fig. 5.—Vaginal epithelium at tenth day of theelin administration (Case 2).

In the earlier cases a bit of the lateral wall of the vagina, 3 to 4 cm. above the hymen, was removed for microscopic examination before and after theelin injections. For this purpose a miniature tonsil punch was introduced through a speculum, a procedure which caused little pain and proved harmless. Normal control sections were also obtained at autopsies from the vaginas of children of different ages. The normal child's vagina is lined with delicate squamous epithelium four to six layers in depth. In contrast, the injection of theelin induces in ten or more days an enormous thickening of the epithelium. From twenty-five to thirty-five or more layers of vacuolated cells are superimposed upon the basement membrane. Often in attempting to obtain a clipping from the vagina after treatment only superficial vacuolated cells were removed, owing to the inability of our small instrument to bite

through the new thickened structure. Our slides show clearly the remarkable changes effected by the theelin which are exactly comparable to Allen's results in the monkey. The presence of desquamated epithelial cells in the vaginal smears was soon recognized as a satisfactory index of the change occurring in the vagina. Consequently in later cases biopsies were regarded as unnecessary.

In monkeys treated with theelin rapid involution to normal of the structures effected occurs when the administration of the hormone is discontinued. In one of our patients a biopsy was taken from the vagina six weeks after theelin was withdrawn. Microscopic study proved that the expected involution had occurred. This process of involution of uterus, vagina, and vulva is, I believe, identical with that which occurs in girl babies shortly after birth.

Fig. 6.—Vaginal epithelium (Case 2) six weeks following termination of theelin administration. Involution is almost or wholly completed.

As previously stated all of our patients were clinically cured when treatment was completed. However, observations were continued even though the vaginal discharge had ceased and the smears had become negative.

SUMMARY OF RESULTS

CASE 1.—Treated with theelin for ten days resulting in apparent temporary cure. Recurred and will be retreated if possible.

CASE 2.—Treated for ten days; apparently clinically cured; followed for seven months with no recurrence.

CASE 3.—Treated for ten days; clinically cured; followed for seven months with no recurrence.

CASE 4.—Treated in hospital for eighteen months with local applications with no effect. Treated with theelin for ten days; apparent clinical cure. Recurred later; treated for twenty-one days with 50 R.U. of theelin twice daily; has remained clinically well with negative smears for two months (to present date).

CASE 5.—Smears negative for gonococci for seven weeks when child was last seen.

CASE 6.—Apparently cured after theelin treatment. Followed four months; no evidence of recurrence; repeated smears negative.

CASE 7.—Clinically well when discharged. Followed five months; no recurrence.

CASE 8.—Clinically well when discharged. Smears negative and no discharge for two months.

A number of cases treated with theelin since those reported have shown like results.

While it is evident from the treatment of so limited a number of cases that guarded conclusions should be drawn regarding the therapeutic value of theelin in the eradication of gonorrheal vaginitis in children, this preliminary study has brought forward two points of importance. In the first place it is of great interest to learn that the administration of theelin produces in the child's vagina a proliferation of epithelial cells identical with that which occurs in the vagina of the immature monkey similarly treated. In the second place it appears that, in the majority of patients, theelin, by inducing a proliferation of the vaginal epithelium, rapidly clears up the discharge and appears to eradicate the gonococci which are causing the infection.

It has been shown that smaller doses of theelin given at short intervals are more efficient than larger doses given infrequently. We plan, therefore, to test the effect of frequent oral administration of the hormone. Should these tests prove successful, we hope to develop a method of therapy more suitable for use in the home.

In conclusion, it should be emphasized that this report is offered solely as a preliminary study. It is our viewpoint also that, until the proper dosage of the hormones and the possible deleterious effects of their administration are understood, they should be employed with caution.

It is a pleasure to express my sense of obligation and gratitude to my coworkers, without whom this study would not have been made. The skill and many hours of labor contributed by Drs. James R. Miller and Ann G. Kuttner were invaluable.

The facilities freely given by Dr. Carl Hartman, as well as his never failing sound advice, helped immeasurably.

Free use was made of the laboratories of the Woman's Clinic in the Yale School of Medicine.

The use of funds granted for bacteriology by the Hartley Foundation to the Harriet Lane Home as well as others from the New Haven Hospital and Harriet Lane Home are gratefully acknowledged.

Parke, Davis and Company supplied, free of cost, the considerable amount of theeline used.

NOTE: Final examination of Cases 5, 6, 7 and 8 dated August 2, July 28, July 26 and July 27, 1933, respectively, i.e., seven to eight months after the conclusion of treatment:

Cases 5, 6 and 8 appear well. Smears are negative for gonococci. No inflammation or discharge present.

Case 7. Slight reddening and discharge. Smears positive for gonococci. Both parents of this child, with whom she has lived since discharge from the hospital, are believed to have a gonorrheal infection.

All hypertrophy of the vulva, etc., caused by the theelin injections has disappeared in these cases.

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52 TRUMBULL STREET

PELVIC (RECTAL) PALPATION OF THE FEMALE MONKEY, WITH SPECIAL REFERENCE TO THE ASCERTAINMENT OF OVULATION TIME*

CARL G. HARTMAN, M.D. BALTIMORE, MD.

(From the Department of Embryology, Carnegie Institution of Washington)

THE rhesus monkey has of late years risen to a station of considerable importance as a laboratory animal. The species is peculiarly adapted for experimentation in medical research, and, of course, is indispensable to students of menstruation and associated phenomena. Any contribution to the technic of handling the animal should prove useful. The rectal bimanual method of palpation which I have applied to the female monkey has proved unexpectedly easy and illuminating. I wish to call your attention to some of the points which the experimenter in the field of reproduction may learn concerning the animal with a minimum of expenditure of time. Special emphasis will, however, be placed on what I have learned concerning ovulation time in this monkey.

1. If it is desired to study phases of pregnancy or parturition in the animal and the time of conception is not known, the stage of pregnancy may be learned with a close approximation to the truth by means of a single palpation and reference to a table which I have prepared on the basis of 20 pregnancies.[1]

2. In experiments involving the ovaries and reproductive tract of female monkeys, as for example, testing the effect of gland extracts or implants, it is most desirable that progressive changes in the organs be followed during the course of the injections. This many of us have, of course, done after a fashion by means of laparotomies; but palpation is almost as convincing and can be done as often as desired. It is possible to ascertain both the size and the changing consistency of the cervix, uterus, ovaries, and even the fallopian tubes with ease and considerable precision by rapid, harmless, rectal palpation.

3. The selection of the experimental animal is furthermore facilitated by the application of the method. To evaluate the results of experiments it is usually necessary to know the physiologic status of the subject—the past menstrual history for example. Monkeys may menstruate, however, quite regularly without ovulating; hence it is usually desirable to ascertain whether a given cycle is going to be or has been an ovulatory or a nonovulatory one. In the one case the ovary enlarges, shrinks, and swells again due to the growth and collapse of the graafian follicle and the growth of the corpus luteum; concomitantly the uterus grows and softens as it never does in a nonovulatory cycle. The reddening of the sex skin is no proof of ovulation. The only externally applicable test for ovulation is, at present, rectal palpation.

*Read, by invitation, before the Fifty-Eighth Annual Meeting of the American Gynecological Society, Washington, D. C., May 8, 1933.

4. As implied in the last paragraph, it is possible to determine the time of ovulation in the menstrual cycle, and it is to this topic that I wish to devote the greater part of my allowance of time.

In 1927, Asdell[2] published a paper on the *Time of Conception and of Ovulation in Relation to the Menstrual Cycle,* and Dickinson[3] likewise ably evaluated the human data in this Journal under the title, *The Safe Period as a Birth Control Measure.* Dr. Dickinson's chart beautifully summarized for the first time the information available five years ago. In the meantime three new methods have been adduced to aid in the solution of the problem: Allen, Pratt, Newell, and Bland added a brilliant chapter to the subject by securing five human ova from the fallopian tube; Knaus furnished the first physiologic test for ovulation in the human subject; and finally, Evans and Swezy attempted to exploit the (still mooted) periodic oogenesis of adult human ovaries as proof that ovulation may occur at any time of the menstrual cycle.

TESTS FOR OVULATION TIME IN WOMEN

Let us briefly outline the tests thus far presented for the ovulation time in women, with a short and therefore necessarily more or less categorical evaluation of the data. I shall state the points in what I consider the ascending order of their validity, the least conclusive "evidence" first.

1. *The Wave of Well-being.*—This is as yet too indefinite to discuss here. The Mittelschmerz phenomenon is interesting but not conclusive.

2. *The Jacobi-von Ott Wave.*—This is related to (1). It involves cyclic changes in basal metabolism, temperature, pulse, and other physiologic phenomena. Only the beginnings of accurate observations have been made in this field. The reports are still most conflicting. It is doubtful whether, in the presence of the complex self-regulating mechanisms of the body (Cf. Cannon's *The Wisdom of the Body*), general somatic changes will very soon be utilizable to establish the exact ovulation time.

3. *The Sex Desire Curve.*—This has more promise, in my opinion, especially in view of results recently attained by Dr. J. Ball in her studies on sex behavior in the Carnegie Monkey Colony. To date, however, the complex factors involved in human sex behavior have not been sufficiently unraveled to separate the physiologic from the psychologic.

4. *A study of cervix, uterus, and fallopian tubes,* histologically or physiologically cannot yield the exact data necessary because of the large margin of variation in the response of an organ even to the same stimulus. Thus, Schroeder's table[4] of distribution in the menstrual cycle of human endometria in various stages of proliferation and secretion is just what one would expect on the basis of Schroeder's assumption of ovulation around the middle of the cycle. By palpating monkeys one gets exactly the same impression of variation in size and consistency of uterus in different animals ovulating on exactly the same day of the cycle. Hence Evans and Swezy[5] are in error in adducing Schroeder's table as proof for ovulation at all times of the cycle.

5. *Sex Hormones in the Blood and Urine:* the female sex hormone (estrin, theelin) and the gonotropic hormone of the anterior lobe (prolan). The pioneer

work of Frank in this direction followed by Kurzcock, G. van Smith, and others, promises to throw light upon the ovulation time, though the results are still too inexact to help us in this problem at the present time.

6. *The Age of Very Young Human Embryos.*—Alas! what is the age of these embryos? The data are for the most part rough estimates, hence usable in connection with the problem only with caution. Monkey embryos of known age, as they are being collected in the Carnegie Colony by Dr. Streeter will, it is hoped, in the near future, by comparison with known human embryos, throw light upon the probable conception age of the latter, and hence also, where the last menstruation is known, upon the conception day with reference to the cycle.

7. *Inspection of Ovaries Intra Vitam.*—Following the lead of Fraenkel many gynecologists have made observations on the state of the ovaries of women laparotomized for other than gynecologic reasons. The author records the days on which large follicles, those on which corpora lutea are found. The probable time of rupture of the former, the probable age of the latter are estimated, and the probable day of ovulation is recorded. In the Dickinson chart it is seen that the estimates crowd pretty well within the interval marked by days 10 and 20. I have made similar observations in the monkey and recorded similar results. By and large, therefore, I am ready to admit that for the most part the data are valid.

There are, however, exceptional cases that are apt to mislead. I have met them in the monkey where, fortunately, I was able to check my observation in a manner not available to the gynecologist. Thus, for example,[6] one female, No. 71, was laparotomized twice within an interval of eighteen days, during which time she menstruated despite the persistence of a 4 mm., somewhat atretic follicle. Hence, who shall say when a follicle under observation is going to rupture or that it will rupture at all?

Again, nineteen days *post ovulationem, post coitum* (therefore *post conceptionem*) Dr. R. R. Squier removed for me a nineteen-day old embryo. The accompanying corpus luteum had the earmarks of a young gland that we should have estimated, except for proof to the contrary, at five to six days, for it was red and it bled on the application of slight pressure.

Such exceptional cases, of which I could cite a not inconsiderable proportion of the total observed, behooves us to go slow in accepting similar ones, without other checks, as proof of ovulation at the exceptional part of the cycle.

8. *Isolated Coitus.*—In my report on *Reproduction in the Monkey,* I reported 55 cases of pregnancy in each of which conception resulted from an isolated coitus.[7] The average conception day was found to be the thirteenth day of the cycle; the great bulk of the cases fall between the twelfth and fifteenth; with the exception of one fertile coitus on the nineteenth day, none occurred outside the tenth to seventeenth days. The conclusion was reached that ovulation takes place in the monkey near the middle of the cycle, never near the menstrual flow. The chief claim to the validity of this conclusion is the fact that the matings were controlled by us; in other words, no allowance had to be made for the subjects' vagaries of memory, lapses from truthfulness, or feelings of prudery.

By innuendo the last statement implies that the corresponding data for women are not so fortunately controlled, as is evident from all the many papers that present original human cases. In view of the fact that this material must be thus discounted, there is no wonder that some cases fall in the premenstruum, the postmenstruum and even in the period of the bleeding. This literature has given gynecologists the confidence amounting to conviction that women may conceive at any time of the cycle. For such a sweeping conclusion even the famous war-time studies of Siegel are no more trustworthy than those of his predecessors. Siegel

questioned parturient mothers in his obstetric clinic and obtained the data of their last menses; from the war-office he obtained the data of the husbands' furloughs. Every day of the spouse's visit Siegel puts down as exposure to impregnation, even if the mate remained as long as eleven days. No wonder that his cases overflow all over the cycle, thus hiding the true fertile period.

These charts, however, allow certain valid deductions: (1) There is a relatively sterile period during the last eight or ten days of the cycle; (2) the peak of fertility occurs several days after menstruation. It will be noted from Dickinson's chart that this peak precedes by a week the average ovulation day as ascertained by laparotomy and the author rightly asks why this is.

The answer to this question would seem to be psychologic. It will be noted that the height of the Davis curve of sex desire parallels the conception curve in the first half of the cycle. Both curves are based on data ascertained by questioning the subjects. The menses themselves and the week or ten days following loom large in the consciousness of women, who therefore are, by and large, more prone to select these days for an answer. The skewness of the curves is, therefore, not physiologic but psychologic.

9. *Uterine Response to Pituitrin.*—Knaus utilized the discovery that pituitrin is unable to cause uterine contractions where there is an active corpus luteum. First tried on rabbits, this principle was found by Knaus to hold for women as well. An active corpus luteum, which abolishes the reactivity of the uterus to pituitrin, is assumed to be three days old, and ovulation is estimated to have taken place three days before the uterus becomes thus refractory. On this basis Knaus never found ovulation to occur in women outside the ninth to the eighteenth days, which corresponds remarkably with my data, to be presented below, in the monkey. The method has been called in question but not as yet disproved by those following the same technic.

10. *Recovery of Ova.*—Positive evidence of ovulation time in women was achieved by Allen, Pratt, Newell and Bland, who recovered tubal ova. From these it could be determined that ovulation took place between the eleventh and the fourteenth day. Lewis and Cullen (W. H. Lewis, 1931) recovered an egg on the twenty-first day of the cycle and estimated ovulation to have occurred about the eighteenth day.

Previous to this, Corner had recovered the first living ova from the monkey, and Allen soon followed with others. All of these findings pointed definitely to the fact that ovulation in menstruating females may be expected to take place very closely about the middle of the interval.

11. *A Final Method of Determining Ovulation Time Is by Palpation of the Ovary.*—While this is impracticable in women, it is quite feasible in the monkey, in which the ovary is perfectly accessible to the palpating finger, and in which the follicle, when ripe, may comprise a large proportion—over half—of the total volume of the ovary. The collapse of the follicle can, therefore, in favorable cases, be noted with great certainty.

OVULATION IN THE MONKEY

This section will be limited to an analysis of 106 cases of ovulation determined by palpation, more particularly to 53 which menstruated after, as well as before, such diagnosis was made. The other half of the 106 cases include pregnancies and animals whose menstrual cycle was interfered with in one way or another after ovulation had taken place.

In Fig. 1 is shown a graph of the 106 ovulations by days plotted on the conventional twenty-eight-day cycle. Each square represents an ovulation, and the number within the square is the accession number of the animal ovulating.

From this graph it is clear that the monkey has a sterile and a fertile period. The ovulation days form a typical Gaussian curve about the thirteenth day as mode, median, and average. Examination of ovulation days of particular animals ovulating more than once discloses a tendency for a given female to repeated ovulations on approximately the same day of the cycle.

The 53 cases thus adapted to comparing the preovulatory and the postovulatory intervals require further analysis, especially in view of Ogino's contention that the latter (the "corpus luteum" interval) is

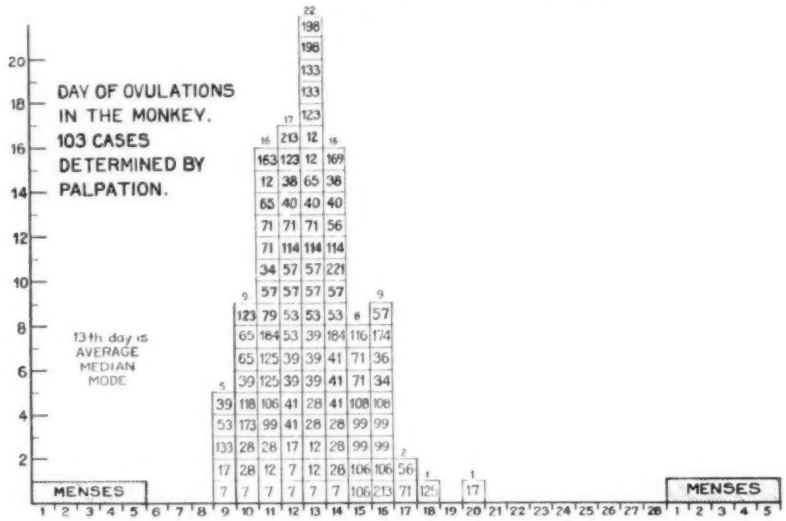

Fig. 1.

the more constant. In 83 laparotomies Ogino never found a ripe follicle later than eleven days preceding the following menses. These eleven days, therefore, constitute a sterile period, regardless of total cycle length. Ovulation, he continues, takes place from twelve to nineteen days preceding the menstrual period. That there is no logic in this interpretation so far as the monkey is concerned will now appear. Since my data are for the present the only precise ones available in numbers for a menstruating organism, it behooves us to follow Ogino with caution.

If, now, we plot at random the menstrual cycles of this series, keeping the ovulation day in a straight vertical column and letting the menstruation days fall where they will, we get the picture seen in Fig. 2. It is apparent at a glance that the postovulation interval, contrary to Ogino, is the more variable. The same fact comes out if we

arrange the cycles in order of total length, from the shortest down to the longest (Fig. 3)—the preovulatory intervals closely parallel the vertical line, the postovulatory intervals become longer as the cycles lengthen. The postovulatory interval contributes much more than its share toward the increased length of the cycle. The same points come out if the cycles are arranged in ascending order of length of either interval (not represented here).

This fundamental fact, that variations in total length of cycles are due to variations in the postovulatory interval, is well shown in the correlation charts in which each moity of the cycle (ordinates) is

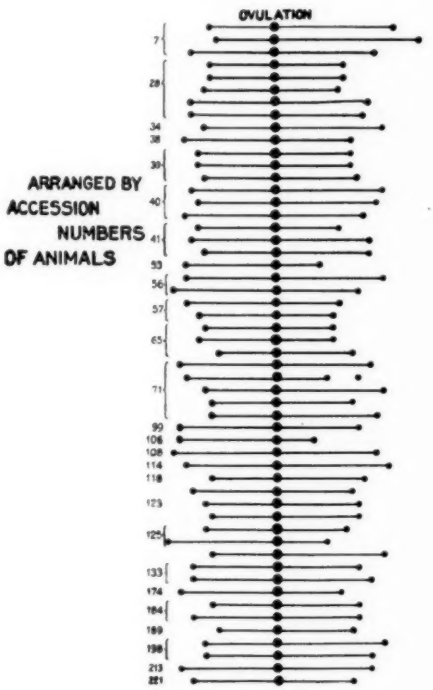

Fig. 2.

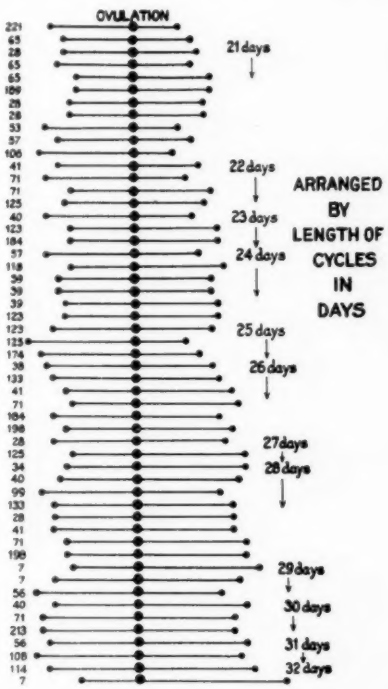

Fig. 3.

plotted against total length (abscissæ), as seen in Fig. 4. It is apparent at a glance that the ratio of preovulatory interval to cycle length is very constant, whereas the latter interval varies with the total length. This is in spite of the great variation in cycle length (top of Fig. 5).

These results, clear-cut as they are, are really somewhat surprising, inasmuch as we have in the past been so much impressed with the importance of the corpus luteum in relation to menstruation. We have come to look upon the growth, bloom, and decay of the corpus luteum too mechanically. Now we find that its life is more variable than that of the follicle before rupture. Two well-known observations may be cited that parallel these new findings: (1) in the rabbit the follicle

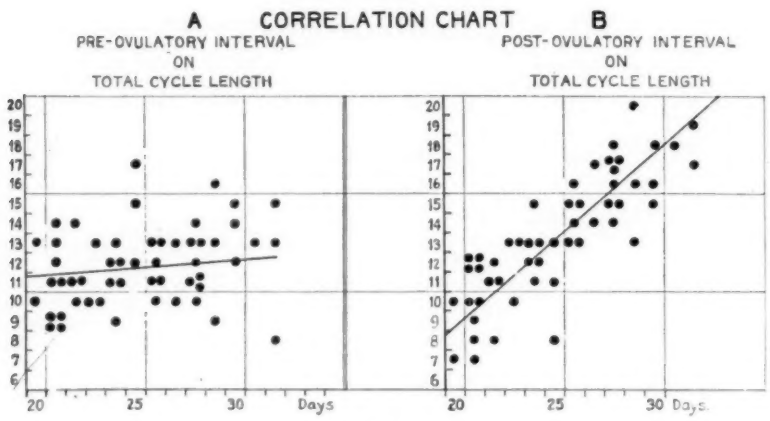

Fig. 4.

completes its growth and ruptures very precisely ten hours *post coitum;* and (2), in the rat the induced pseudopregnancy or corpus luteum phase is most variable, ranging from eight or nine to twenty or twenty-one days.

A question naturally arises: Are the facts thus accurately ascertained in the monkey to be transferred to man? In other words, is

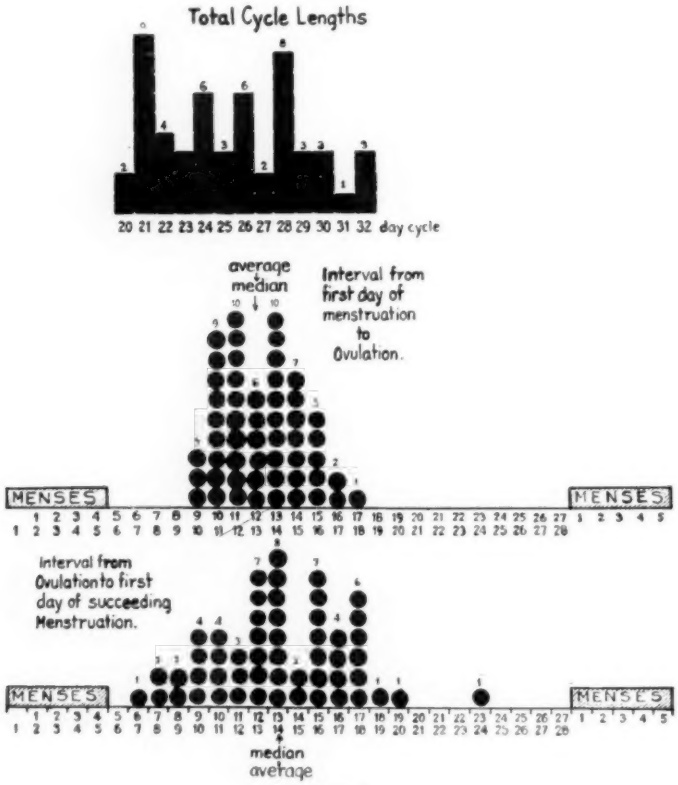

Fig. 5.

Ogino right or wrong? Certainly a female monkey, desiring to use the "safe period" as a contraceptive measure, would, in view of the facts, not think of counting back from the next following menses even if she could predict exactly when this was to take place. The matter is of very considerable importance from the standpoint of human welfare inasmuch as many now advocate the "natural method" of birth control (avoiding the fertile period). Physicians, too, must advise patients who have religious scruples against the use of contraceptives—persons who would prevent germs from passing into their windpipes, but who balk on preventing sperms from passing into their oviducts!

Two considerations would seem to warrant gynecologists giving thought to these data based on the monkey: (1) the cycles considered were all characterized by ovulation, hence the succeeding menstruation was a "true" menstruation; and (2) there exist no comparable data for women—not a single reliable case. Until such are forthcoming, it seems to me we might let animal experimentation guide us, particularly since all the other phenomena accompanying menses in the monkey are so very much like those in man.*

SUMMARY

1. The evidence on ovulation time in women is briefly scrutinized in the light of present knowledge of reproductive processes and in the light of common sense.

2. The first definite proof of ovulation time in primates we owe to Corner and Allen; in man to Allen, Pratt, Newell and Bland, who recovered ova from the fallopian tube. Ovulation occurred in their cases near the middle of the cycle.

3. The physiologic test of Knaus gives great promise of general human applicability. The evidence points to days 9 to 18 as the ovulation days in women.

4. Over 100 precisely determined cases of ovulation in the monkey occurred almost altogether on the tenth to the fifteenth days, a few on other days. The monkey has a long "safe" period. Much corroborative evidence, such as 55 cases of isolated coitus, has been previously published by the writer.

5. An analysis of 53 cases, in which ovulation was recorded in completed cycles, shows that the preovulatory interval is relatively constant and that the variations in total cycle length parallel and are due almost altogether to variations in the length of the postovulatory interval.

*Thanks are due to my colleague, Dr. J. Ball, for statistical analysis of the data, and the preparation of the correlation chart, Fig. 4.

6. Ogino's suggestion that we count backward from the succeeding menstrual period to determine the ovulation day need not worry us at present, at least until it can be shown that man differs from monkey in this respect, which is not likely.

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ADVANCED CARCINOMA OF THE CERVIX, WITH A REPORT OF 166 NECROPSIES*

Charles A. Behney, M.D., Philadelphia, Pa.

(From the Gynecologic Service, Radiologic Department, Philadelphia General Hospital)

More than 75 per cent of all patients with carcinoma of the cervix die, either directly or indirectly, as a result of the disease. When the condition becomes definitely incurable, interest in its terminal manifestations is frequently lost.

In the belief that it might be possible to secure some additional information of practical importance concerning the ultimate pathologic changes which occur in patients with carcinoma of the cervix, the present study was undertaken. It deals with three main topics: (1) The cause of death, (2) the extent of the disease, and (3) the effects of irradiation.

The study is based upon the histories and the necropsy records of 166 patients who died in the Philadelphia General Hospital. It includes all postmortem reports which were made between the time that the Radiologic Department was organized in 1922 and Dec. 31, 1932.

Several points should be emphasized: Of the 166 patients, 80 had received no treatment, the remainder had been irradiated with varying amounts of either radium, high voltage roentgen therapy, or both. All diagnoses of carcinoma of the cervix were based upon histologic study of the primary tumor. Routine postmortem examination was limited to exploration of the thorax and abdomen. Microscopic examination of *all* pelvic tissues was often impossible because of widespread infection and

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necrosis. All extrapelvic organs which exhibited any gross pathologic changes were studied microscopically.

CAUSES OF DEATH

The immediate causes of death may be grouped according to their relation to the carcinoma, and again as to whether they are extrapelvic or intrapelvic in origin. In only 7 (4.0 per cent) of the cases was the cause of death *not* related to the carcinoma. These included 4 patients with heart disease, 2 instances of cerebral hemorrhage and one patient who died of acute pancreatitis.

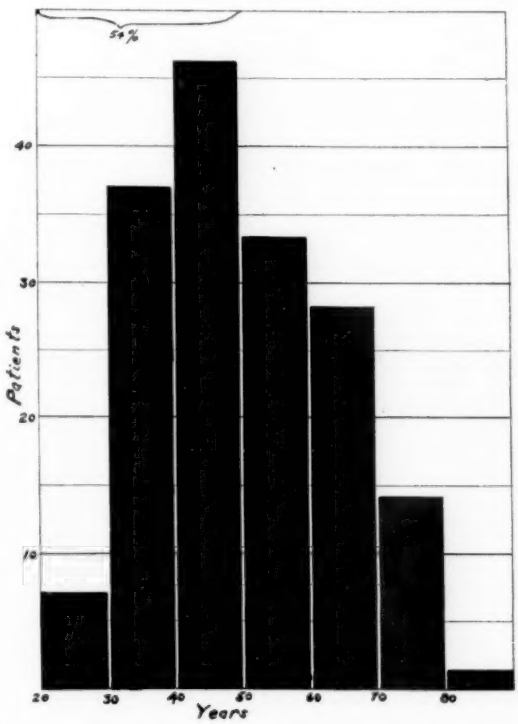

Fig. 1.—Graphic presentation showing the age of patients on admission.

One hundred and fifty-nine deaths (96 per cent) could be directly related to the carcinoma. These were almost equally divided between those of extrapelvic (80) and those of intrapelvic origin (79). The extrapelvic causes included terminal pneumonia, which occurred many times, and such rather vague causes as cachexia, asthenia, and exhaustion. To draw a sharp line between extra- and intrapelvic causes, dependent upon the presence of the carcinoma, is impossible. This division was employed merely to facilitate the presentation of the material.

The intrapelvic causes are classified as septic causes and as mechanical causes, the latter including hemorrhage. We regarded the septic condi-

tions as having originated in the neoplasm, and they were sometimes generalized as well as localized. Septicemia occurred 5 times. Localized septic processes in the liver, the lung and the perinephric region were found in 7 patients who exhibited no evidence of generalized blood stream infection.

Two women died from suppurative parotitis. We have also observed parotitis as a terminal condition in a number of patients with advanced carcinoma of the cervix upon whom necropsy was *not* performed.

One patient died from gangrene of the leg which followed an infected thrombus of the femoral vein. Four patients died of general peritonitis. In two of these cases, the carcinoma had eroded into the peritoneal cavity; and in one instance, the uterus had been perforated with an instrument. The fourth case of peritonitis was ascribed to the reactivation of a quiescent pelvic infection as a result of radium irradiation.

Mechanical Causes of Death.—In 60 (36 per cent) of the 166 cases, death was due to mechanical causes. The most common one was ureteral obstruction, which operated by bringing about a fatal uremia in thirty-six women, or 21 per cent of the entire group. Other mechanical causes of death were involvement of the lower bowel, observed in 7 cases, and fatal hemorrhage which took place in 15 instances.

Relation of Age to Cause of Death.—The 166 patients were almost equally divided between those who were over fifty years of age (46 per

TABLE I. DISTRIBUTION OF METASTASES

		NUMBER	PER CENT
Abdomen:		53	60
Liver	17		
Paravertebral nodes	16		
Ileum	4		
Peritoneum	3		
Cecum	3		
Omentum	2		
Colon	2		
Kidney	2		
Pancreas	1		
Stomach	1		
Spleen	1		
Adrenal	1		
Thorax:		22	25
Lungs	17		
Diaphragm	2		
Mediastinum	2		
Pleura	1		
Skeleton:		13	15
Pelvis	6		
Vertebras	5		
Femur	1		
Skull	1		
Total		88	100

cent) and those who were less than fifty years of age (54 per cent) (Fig. 1). In general, it was observed that deaths from infection were twice as frequent in the older women as in the younger ones.

EXTENT OF THE DISEASE

There were 88 metastatic lesions (Table I); these occurred in 55 (33 per cent) of the 166 patients. They were found in only 17 (21.2 per cent) of the 80 *treated* patients but in 38 (44 per cent) of the 86 in the *untreated* group. Their anatomic distribution was the same in both groups.

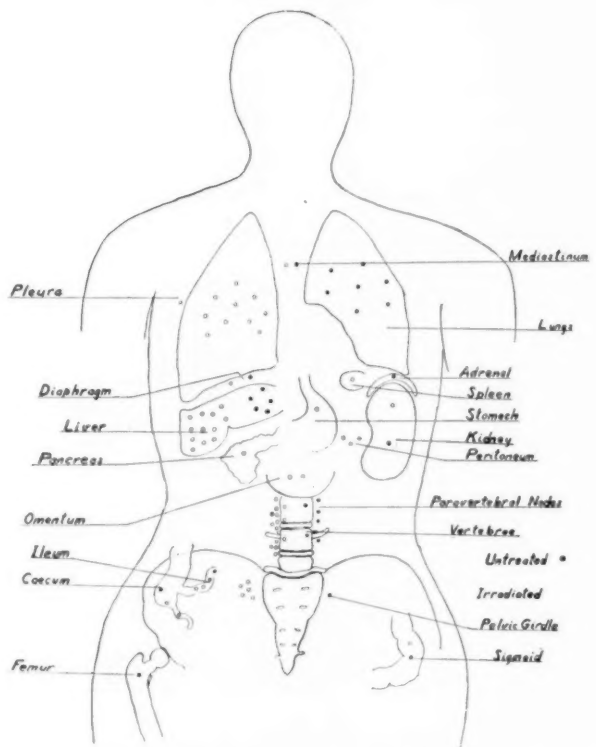

Fig. 2.—Diagram illustrating the frequency and distribution of 88 metastases observed in 55 patients. Growths in untreated patients are designated by a circle (o); those in treated patients by a dot (.). The descriptive signs of the lesions are located without reference to the part of the organ which was involved. Note the lesions in the right temporal bone and the right femur.

The distribution and frequency of the 88 lesions are recorded graphically in Fig. 2. It will be noted that the majority (60 per cent) of all metastatic lesions occurred within the abdomen. It will be seen also that the liver, paravertebral nodes and lungs were the organs most frequently involved and accounted for 50 of the 88 metastases. Twenty-five additional metastases were scattered among the various organs, chiefly those within the abdominal cavity. There were 13 bone lesions, one occurring in the right temporal region.

Three methods of dissemination of carcinoma are illustrated in this series: (1) A temporal metastasis is probably an example of blood stream distribution. (2) The pelvic bone metastases illustrate extension by direct continuity. (3) Visible and palpable enlargement of the lymphatics leading from the primary tumor to secondary growths in the stomach, diaphragm, mediastinum, pancreas, and kidneys indicated dissemination through these channels.

Dense carcinomatous masses were observed frequently in the vicinity of the promontory of the sacrum. Many of the most important lymph channels and sympathetic nerve fibers from the cervix pass through this area. Dr. Philip Custer, the Hospital pathologist, has found frequently at autopsy carcinoma cells involving, not only the lymphatics of this

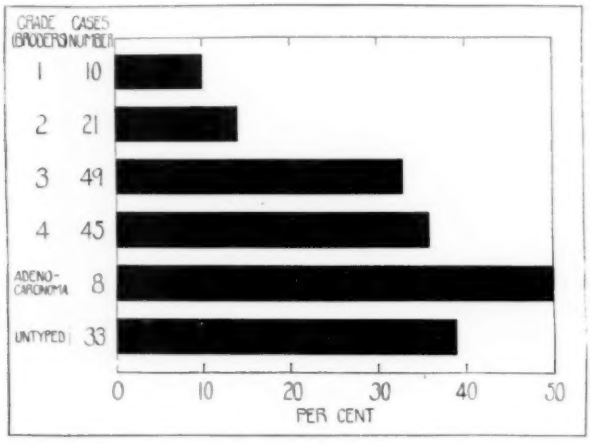

Fig. 3.—Metastasis and cell type.

region, but also the sympathetic nerves. In some instances his specimens were secured from patients, who had suffered great pain, which was relieved after extirpation of these nerves. The usual findings were permeation of the perineural lymphatics, invasion of the nerve itself, and at times destruction of the nerve fibers.

The relation between the histologic type of the tumor cell according to Bröders' classification, and the frequency of metastases is recorded in Fig. 3. Of the 166 subjects, 158 exhibited squamous cell carcinoma and 8 had adenocarcinoma. The incidence of metastases increased with the degree of anaplasia. These observations coincide with those of Bröders' who also found that the more anaplastic types of tumors have a greater tendency to metastasize. Shields Warren found visceral metastases in 67 per cent of 18 patients with anaplastic tumors, as compared with 4 per cent of 23 patients with the adult type of carcinoma of the cervix.

EFFECTS OF IRRADIATION

Fistula Formation.—The incidence of vaginal fistulas is shown in Table II. It will be noted that fistulas occurred in 21 (26 per cent) of the 80 irradiated, and in 27 (31 per cent) of the 86 untreated patients. They were less frequent in the treated patients and vesicovaginal fistulas occurred more than three times as often as the rectovaginal variety.

TABLE II. INCIDENCE OF FISTULAS

PATIENTS		VESICOVAGINAL	RECTOVAGINAL
TREATMENT	NUMBER	NUMBER	NUMBER
Irradiated	80	15	6
Untreated	86	22	5

Ureteral Dilatation.—Dilatation of the ureters was found in 108 patients, or in approximately 65 per cent of the entire series. It occurred in 58 per cent of the irradiated and in 72 per cent of the untreated patients. The frequencies of fistulas and of ureteral dilatations were less in the treated (58 per cent) than in the untreated group (72 per cent).

Untoward Effects of Irradiation.—Three patients after intensive irradiation deteriorated very rapidly and died. At necropsy, there was extensive sloughing of pelvic structures in all of them. In only one, however, could any trace of carcinoma be found and this was a very small area upon the adventitia of one ovarian artery. These deaths appeared to be due to a sudden and overwhelming intoxication, probably the result of too vigorous treatment.

SUMMARY AND CONCLUSIONS

This study has brought out several interesting facts regarding the terminal manifestation of carcinoma of the cervix. Only 7, or 4 per cent, of the 166 patients died from causes which were not dependent upon the presence of the cancer.

In the older patients, death was caused by secondary infection twice as frequently as in the younger ones. In the latter group, death was more often the result of some mechanical cause such as obstruction of the ureters or hemorrhage.

Metastatic lesions were observed in the lungs just as frequently as in the liver.

The more anaplastic the type of tumor, the more frequently did metastasis occur.

Involvement of the pelvic sympathetic nerves has again been demonstrated. This involvement may be a factor in the production of pain, and suggests that the interruption of impulses through these nerves by invading tumor cells may be the explanation for the occasional spontaneous disappearance of pain in patients with advanced disease.

The extensive necrosis following intensive irradiation of three patients demonstrates the danger of such irradiation in advanced carcinoma of the cervix.

Due acknowledgment is here given to the Pathologists of the Philadelphia General Hospital for their cooperation in the preparation of the material for this report.

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133 South Thirty-Sixth Street

FURTHER STUDIES OF THE FASCIAL PLANES SURROUNDING THE VAGINA*

Nathan P. Sears, Ph.B., M.D., F.A.C.S., Syracuse, N. Y.

(Associate Professor of Gynecology, Syracuse University)

IN A recent paper[1] describing my gross dissections of the pelvic fascia, I stated that the vagina is surrounded by definite layers of fascia, that these layers are attached to the pelvic floor by a broad main sheet (endopelvic fascia) and that the whole structure is a continuous reflected layer from the superior levator fascia. While I was engaged in my first dissections, Goff[2] in an excellent and complete study of the fascial planes of a nulliparous pelvis, showed the value of microscopic study in working upon this important anatomical problem.

This present study is based upon the partial dissection of the pelvis of a young virgin and autopsy specimens from two infants and one adult nullipara.

The dissection of the cadaver specimen was limited to the removal of the peritoneum together with the tubes, ovaries, rectum and uterine body. The fat was then scraped out with a blunt instrument. The arrangement of the main sheet of fascia agreed with the description of my former dissections. Special attention was given the blood vessels which supply the vagina and bladder. These extend along the superolateral surface of the main sheet. Those supplying the vagina bend medially until they reach a point just lateral to this organ where they penetrate the fascia (Fig. 1). Owing to the fact that the vessels of this specimen were not injected they cannot be easily traced further in the gross but their distribution will be noted in the microscopic sections.

*Read at the Fifty-Eighth Annual Meeting of the American Gynecological Society, Washington, D. C., May 8 to 10, 1933.

The autopsy specimens included the uterus, vagina, bladder, rectum and as much of the other pelvic tissue as it was possible to obtain. The entire structure was then hardened in formalin and preserved in alcohol. The rectum, bladder and most of the pelvic connective tissue were removed. My first plan was to make a gross dissection of the fascial planes before cutting the blocks for microscopic study, but this produced so much damage that it was abandoned. Since it has previously been shown[1, 2] that no plane of fascia exists between the urethra and the vagina, transverse sections were taken only at various planes between the level of the internal urethral meatus and the cervix. These were prepared according to the usual celloidin technic and stained with hematoxylin, eosin, and orange G for connective tissue contrast.

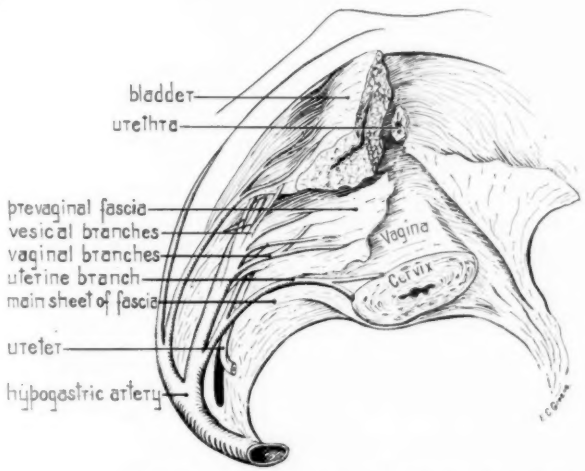

Fig. 1.—Semi diagram of left ventral quarter of partially dissected pelvis of young virgin. It shows the relation between the blood vessels and main sheet of fascia. Also the manner in which the vaginal vessels penetrate the prevaginal fascia.

Autopsy Specimen 1: Adult nullipara, aged twenty-eight years (Fig. 2). At the periphery of this section are broad bands of loose areolar fascia of the type usually found between the various pelvic organs and which, therefore, do not pertain to the present study. Immediately adjacent to the posterior vaginal wall is a compact band of connective tissue which can be traced across the width of the vagina and laterally for some distance beyond the vaginal wall (Fig. 2, *a-a*). The portion of this band lying next to the vaginal musculature contains within its substance prominent blood vessels (Fig. 3). The location and arrangement of this layer together with the fact that it takes the characteristic stain of connective tissue, is sufficient evidence to mark it as the basic structure of the retrovaginal fascia, and that it is an extension of the medial leaf of the main sheet (Fig. 4).

The anterior wall presents a different appearance. At a point lateral to the vagina, between the broad bands of areolar tissue and just above the lateral extremity of the retrovaginal layer is a narrow band of dense connective tissue (Fig. 2, *b*). The location and structure of this seems to indicate that it is a section of the prevaginal fascia extending medially from the main endopelvic layer. As this band extends toward the anterolateral vaginal wall it widens to surround the cross-section of a large vessel (Fig. 2, *c*). This is evidently the point at which the

vessels penetrate the prevaginal fascia. From this point medially, the major portion of this structure, which is composed of rather large blood vessels closely surrounded by dense connective tissue (Figs. 5 and 6) extends over the anterior vaginal wall and a lesser portion bends backward to blend with the retrovaginal fascia. As the anterior plane extends medially, it thins out to a narrow band surrounding a single layer of blood vessels (Figs. 2 and 6). In the sections the connective tissue is stained a bright yellow, in the illustrations muscle may be dif-

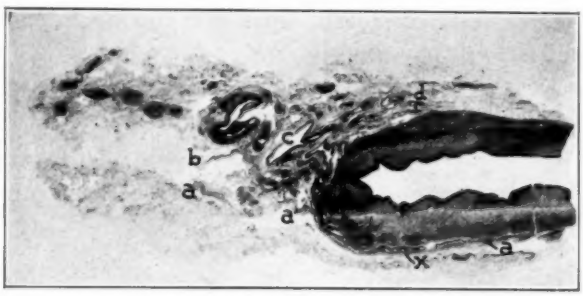

Fig. 2.—Transverse section of adult vagina, midway between cervix and level of internal urethral meatus (×3). Surrounding the cavity of the vagina is the epithelium which appears as a dark line. Immediately peripheral to this is a paler area, the tunica propria, peripheral to this appears the muscular walls, recognized by their coarse fibers and darker color. The muscle on the anterior wall is thicker than that on the posterior wall. Adjacent to the muscle on the posterior wall is the retrovaginal fascia (*a'-a*), a narrow band containing blood vessels in its structure. It extends well past the wall of the vagina where it becomes part of the main sheet (*a'-a*). Above at "*b*" the other layer of the main sheet approaches the vagina. A short distance to the right it spreads out into a thin dense layer surrounding blood vessel (*c*). From here medially the structure is a sheet of fibrous tissue surrounding blood vessels, tapering toward the midline.

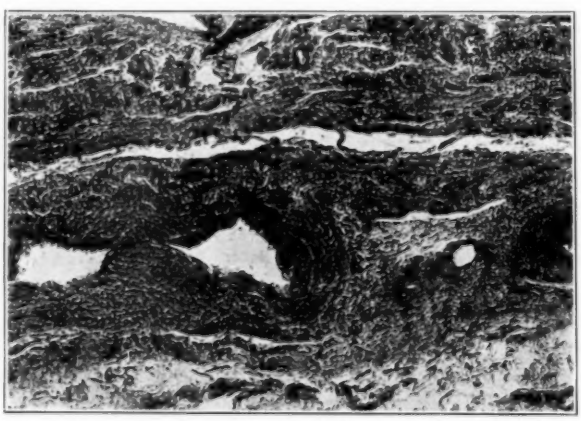

Fig. 3.—Higher magnification (×62) of retrovaginal layer at "*x*," Fig. 2. Crossing just above the center of section is a clear space. Above this is the muscle and below the layer of fascia. The character of the fibers is distinctly different and in the slide the fascia is yellow, the blood vessels dark. Immediately below the fascia are loose areolar fibers.

ferentiated from fascia by the darker appearance of the former and its coarser texture.

Autopsy Specimen 2: Infant twenty-two months old. In a transverse section through the cervix, vagina, perivaginal tissue, and rectum (Fig. 7), a dense band of fascia, the main sheet of pelvic fascia, is seen extending past the rectum toward the lateral margin of the vagina. It has a slight tendency to take the form of two

bands (medial and lateral leaf of the main sheet) and, as it reaches the vagina, its fibers divide to pass anteriorly and posteriorly to that organ. Some fibers penetrate into the developing musculature (Fig. 8). In the stained slide they are seen as tapering yellow bands. The blood vessels, although small, are intimately associated with the fascia. The fibers of fascia do not extend across the entire width of the vagina but taper off at about the junction of the middle and lateral thirds.

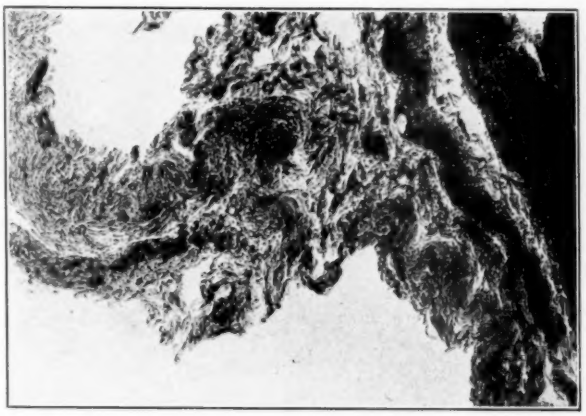

Fig. 4.—(Magnification ×62.) Extending from the left is a curved band of connective tissue made up of dense fibers, the retrovaginal layer, arising from the main sheet and blending (right) with the posterior vaginal wall. A large blood vessel (right center) lies against the vaginal wall. (Taken at *a'* Fig. 2.)

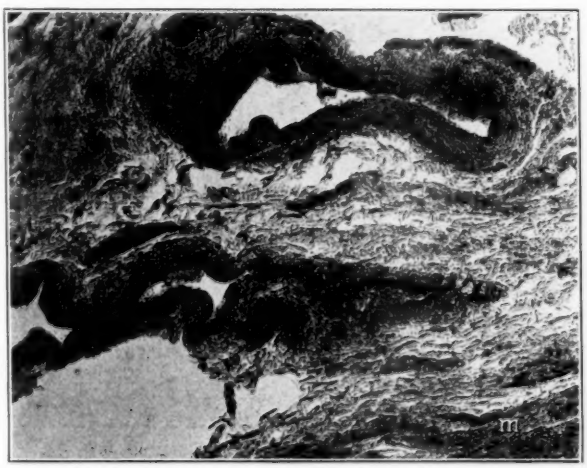

Fig. 5.—Section through anterior wall at "*d*" (magnification ×62). Here are two large vessels surrounded by dense fibers of connective tissue. At lower right is a triangular area of vaginal muscle (*m*).

Autopsy Specimen 3: Eight-month-old infant, dying of Hodgkin's disease (Fig. 9). The same general arrangement of the connective tissue elements is seen here as was described in the preceding specimen. The endopelvic sheet is more fragile in appearance and definitely separated into two layers, the lateral one containing a diseased lymph gland. Over the peripheral surface of the muscle, a few of the fibers of which are separated from their original location, are seen thin fibers of connective tissue definitely continuous with the fibers of the main layer.

DISCUSSION

It is not possible, from the study of so small a number of specimens, to answer many of the debated questions regarding such a complex subject as the pelvic fascia. Some of these questions have already been answered in the many publications; some still await solution. In my first article on this subject, I stated that the main sheet of pelvic fascia

Fig. 6.—Section of adult vagina (magnification ×3). Here the same general arrangement as in Fig. 2 except the prevaginal layer is seen to extend as a narrow band to the midline.

Fig. 7.—Section through cervix, vagina, rectum, and connective tissue of a twenty-two-month-old infant (magnification ×3). Above is the section of vagina, surrounding a section of cervix. Below is the rectum. To the right of the rectum extending up to the lateral border of vagina is a dense narrow band composed of two layers. At the margin of the vagina fine fibers from this band pass anteriorly and posteriorly over the surface of the vaginal musculature. Some penetrate the muscle. At the extreme top of section, a fine layer is seen dissected from the surface, and to the left muscle bundles are also dissected away. On the posterior wall at the right some muscle is also dissected away. The left border of the section is less clear because of gross dissection. Arrows indicate area of Fig. 8.

was a continuation of the fascia covering the superior surface of the levator ani muscle. This statement is quite opposed to the opinions of many and awaits confirmation. It is, however, a very important

matter. Now that it has been shown that the fascial planes around the vagina are derived from this main sheet, proof that the main sheet is a true fascia would prove the others so to be.

Fig. 8.—Taken from section 7 at "arrows" (magnification ×48). Here intermingling bundles of fascia and muscle are seen. At the top is a definite band of connective tissue and a few narrower bundles at the bottom. This section shows well the relation of fascial fibers with the muscle.

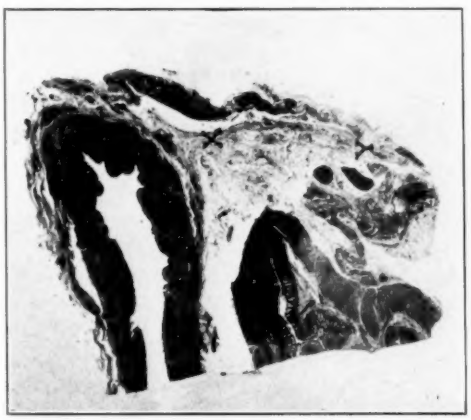

Fig. 9.—Section of vagina, rectum, and fascia of eight-month-old infant (magnification ×3). Above is the vagina. Its darkly stained walls are easily identified. Below is the rectum. The plane of fascia to the right, much more delicate than in the other specimens, is recognized at "*x-y*." Following past the lateral wall of the vagina are a few fibers. The fine pale lines of connective tissue are also seen anterior and posterior to the muscle. Extreme right center is a diseased lymph gland.

CONCLUSIONS

1. There is a broad plane of fascia arising from the pelvic floor to meet the lateral margin of the vagina.

2. There are layers of connective tissue planes laid down upon the periphery of the vaginal muscle which are continuous with and derived from the main sheet of fascia.

3. At the posterior wall this plane of tissue is a more compact unit than that on the anterior wall, the latter appearing to be a mass of fibrous bundles accompanying the blood vessels.

4. The general framework of the pelvic fascia is laid down as early as the eighth month of life and the density of its component parts increases as functional demands are placed upon it.

5. Finally, therefore, the basic structure of the perivaginal connective tissue, no matter what other tissue accompanies it during dissection, is composed of fibrous bundles from the main sheet of the endopelvic fascia.

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505 MEDICAL ARTS BUILDING

NOTE: It was not possible to publish in this issue of the *Journal*, all of the papers read at the Fifty-Eighth Annual Meeting of the American Gynecological Society. Those omitted, together with the discussions, will appear in subsequent issues.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK

Reviews of New Books

GYNECOLOGY

Judging by the first volume of this most recent addition to American textbooks, *Obstetrics and Gynecology*,[1] this should be a series of which American gynecologists and obstetricians may well feel proud. The entire work is to consist of three volumes.

Volume I which contains 1165 pages, deals largely with obstetrics. Even so, it is noticeable that every effort to avoid padding and to favor condensation, has been made. The preface of the editor bespeaks a remarkable self-restraint, covering exactly one-quarter of a page. The list of contributors contains a carefully selected group of all the best names in the special field of obstetrics and gynecology in the United States. In addition, special talent has been enlisted among embryologists, physiologists, etc.

A fascinating chapter on the history of midwifery in America and the birth of gynecology has been contributed by Irving S. Cutter, lavishly illustrated, among them some very rare prints. This occupies 190 pages.

The anatomy of the soft parts by Barry J. Anson has great value because of the many original illustrations made from dissections to accurate scale and modified from information obtained on the living subject during operation. It is a great pity that these illustrations have been reduced to one-third as their originality and excellence warrant them to be full size. They are of sufficient importance to justify separate appearance in the form of a brief atlas.

Adair deals with the bony and ligamentous pelvis in a short chapter.

Novak has taken a very active part in the first volume. The subjects he covers are the physiology of the reproductive organs exclusive of pregnancy, including a historical review; the clinical characteristics of normal menstruation; puberty and precocious puberty; the menopause; cyclical changes in the ovary. These chapters, although short, are clearly written, include our rapidly changing views, and are adequately illustrated. Together with Hartman, he discusses menstruation in the light of the newer knowledge dealing with the physiology of reproduction.

Hartman describes the reproductive cycle in animals.

Section III of this first volume embraces the morphology and physiology of pregnancy, the first chapter covering the maturation and fertilization of the ovum by Hartman and Patten. No more striking diagram was ever supplied than that showing the relative size of mouse, man and whale and the comparatively small difference in size of their ova. The complicated subject matter has been simplified as much as possible. The early development of the embryo is taken up by Patten and Hartman and includes photomicrographs of the fertilized ovum of the monkey and rabbit embryo in vivo. The early embryological changes in the human are based on the well-known Miller embryo.

[1] **Obstetrics and Gynecology.** Edited by Arthur Hale Curtis. W. B. Saunders Co., Philadelphia, 1933.

Placentation, fetal membranes and decidua are described by Leslie Brainerd Arey. The diseases of the embryo and appendages are discussed by Edward A. Schumann. Just why this chapter and the next on the anatomy, physiology and pathology of the fetus by Adair and Schumann, have been interpolated between normal conditions, is not apparent.

The embryology of the female generative tract (Arthur K. Koff) takes into consideration all the newer acquirements of recent years, with the exception of the development of the ovary in which the origin of the germ cells is dealt with in a slightly one-sided fashion. It would seem warranted to give greater emphasis to the theory of those who believe that definite proof has been supplied of the extra embryonal origin of the primordial cells, for example the work of Danchakoff, which has not even been mentioned.

The main portion of what follows is roughly half of the first volume and deals with the clinical aspects of obstetrics beginning with the presentations of the fetus by David S. Hillis.

Lack of space prevents little more than enumeration of these chapters, all of which are fully adequate. The maternal changes which are incident to pregnancy are discussed by Hofbauer who first pointed out the defensive mechanism appearing in the broad ligament during gestation. The diagnosis of pregnancy has been written by Otto H. Schwarz. It seems to me justified to dignify the pregnancy test of Friedman by a special name because of its extreme importance and utility and because it is rapidly displacing the original Aschheim-Zondek technic, as well as to place the reference to the original article in the bibliography.

The management of normal pregnancy (prenatal care) is by Danforth, including a section on vitamins in pregnancy by Urner. Much useful information will be found in this discussion.

The physiology of the birth processes is covered by John W. Harris and Madeline J. Thornton.

Section V deals with labor. The mechanism of vertex presentation is taken up by Schumann. The conduct of normal labor is dealt with by Baer who points out that although labor is the high point in a series of physiological processes, every woman in labor is a potential emergency major surgical risk. Danforth describes the puerperium, including the histology of this important period.

Section VI has the newborn child as its subject, by Arthur H. Parmelee, while the changes in the fetal circulation following birth are taken up by Patten. Irving F. Stein deals with multiple pregnancy.

Section VII covers the pathology of pregnancy. The chapter on maternal illness complicating pregnancy is written by William S. Middleton, special attention being directed to the endocrine system. Among pituitary troubles during pregnancy I would suggest that in a succeeding edition, disturbances of vision as well as exaggeration of physiological acromegaloid processes be added. Greater caution should be used in outlining the indications for allowing pregnancy in tuberculous patients as the general practitioner is too apt to be guided by the period of quiescence which has elapsed rather than the resistance acquired by the patient. The chapter on toxemias of pregnancy has been written by Mussey and Randall.

A. M. Campbell describes the disturbances due to the diseases and abnormalities of the female genitals, which include malpositions, congenital anomalies, newgrowths and pelvic infections in connection with pregnancy.

The final chapter is by Litzenberg on spontaneous abortion and premature labor. I cannot agree with him that the treatment of missed abortion need be active. On the contrary, I know of no condition in which conservatism is more readily crowned by success. At the utmost, a few doses of pituitrin should suffice.

Volume I is equipped with a complete index of its contents.

In this very summary review of the contents of Volume I, which is necessitated by its size and completeness, full justice to the value of the contribution is hardly possible. In general it may be said that the standard is high, although certain chapters stand out because of the greater care and originality of the text. Throughout the illustrations are profuse and adequate. Many are from well known sources, to which due credit has been given, but a large number are original.

A bibliography concludes each chapter. No uniformity in bibliography has been adhered to, some being alphabetically arranged, others not. On the whole, the bibliography is less complete than a book of this high grade demands.

All in all, I may repeat, that if the succeeding two volumes keep up to the present standard, this will be an outstanding contribution to the literature of gynecology and obstetrics in the English language.

R. T. FRANK.

The report of the Bellevue-Yorkville Health Demonstration of New York City, aided by the Milbank Memorial Fund, is an important preliminary contribution to the study of cervico-vaginitis of gonococcal origin in children.[2] Doubtless the term cervico-vaginitis is used in order to focus attention to the frequency with which the cervix is involved.

Two previous investigations, the first one in 1927 by the Charity Organization Society and an independent committee preceded this study which has a threefold aspect, purely medical, bacteriological, and social.

Brunet and Tolle give the medical report which is based on a study of 241 cases of which 172 were subjected to vaginal endoscopy through a simple straight endoscope of 26 to 28 French charière.

In these 241 patients, 192 were shown to have gonorrhea either by spread or culture; 33 proved suspicious; and 37 were found negative. The clinician and the laboratory agreed in 85 per cent. Of importance is that of 113 cases investigated, one or more other members of the same family were found to have gonorrhea with the high incidence of 92 per cent. In the fewest instances did sex contact or violation cause the trouble. The medical investigators found that hospitalization was rarely needed. In none of the cases was peritoneal infection or rectal infection noted.

Only 34 patients were treated with vaccines, the majority responding to local chemotherapy of various kinds.

It appears to me that undue emphasis is placed upon simple cleansing of the parts which of course is essential for both the comfort and hygiene of the patient but in itself cannot be regarded as a curative measure. My personal experience in more fortunately situated children has shown that endoscopic treatment of the cervix and urethra, in the great majority of cases, eventually brings about a complete cure.

In the bacteriological investigation a modified gram stain was devised, which partakes both of the qualities of the Gram and of the Pappenheim method. Of 300 cases, 3 showed a gram negative diplococcus which was not a gonococcus.

The social service aspects emphasize the need of better facilities for special treatment of these patients.

This monograph is a valuable contribution to an important and often neglected field which is usually dodged, if possible, by the gynecologist and pediatrician.

R. T. FRANK.

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[2]**Cervico-Vaginitis of Gonococcal Origin in Children.** Report of a Project of the Bellevue-Yorkville Health Demonstration of New York City. By W. M. Brunet, D. M. Tolle, S. A. Scudder and A. R. Medcalf. Foreword by E. D. Barringer, R. L. Dickinson and W. H. Park. Reprinted from Hospital *Social Service Magazine*. Supplement No. 1, March, 1933.

This monograph[3] on gonorrhea is a very fine presentation of the subject. The book is offered primarily for the practitioner who has had little special training in the disease and its therapy. The general characteristics of the gonococcus are followed by a full consideration of the pathology and symptomatology of gonorrhea. Treatment is taken up in the remaining third of the book. The life of the gonococcus is discussed in the first chapter, the cultural and tinctorial reactions in differentiation are given. A color plate shows the characteristic nonhemolyzing growth of the gonococcus as contrasted with M. catarrhalis and meningococcus. The failure of the agglutination reaction is brought out.

The pathology and symptomatology of the disease follows the gonococcus from the vulva to the peritoneum with all its by-excursions, complications and effects, subjective and objective. The author remarks that aside from the usual acute onset of symptoms, gonorrhea has a frequent tendency to begin as a chronic disease. He feels that pyelitis and pyelonephritis are seldom due to the gonococcus, and are usually complications from associated organisms such as streptococci and *B. coli*. The rectum he has found involved in 20 per cent of his cases, a severe inflammation, never going high up in the canal, and without stricture formation, as a rule.

The protective mechanism of the vagina, the latency of the disease in the cervix and its mode of ascent are described. The latency is paralleled by the experimental analogy of preserving living cultures of gonococci under paraffin or oil for long periods of time. This latency is well marked in the so-called symptomless cases.

He differentiates between the bleeding of endometrial infection and ovarian dysfunction produced by the organism, and discusses their relation to alterations in the cycle. The limitation of the disease to the pelvic peritoneum is explained and the observation of Villard comparing the abundant serous exudate of the pelvis to the pretuberculous pleuritic effusion is repeated. The infrequency of parametritis is discussed. Metastatic manifestations of gonorrhea are not considered germane to the book. The differential diagnosis covers, one might remark, the pathology of the entire lower abdomen. There are well written sections on gonorrhea complicating pregnancy, and gonorrhea of children. A chart is inserted to illustrate the reactions of the puerperium caused by the gonococcus, and their dissimilarity to sepsis.

The author mentions the racial differences seen in gonorrheal disease; the unusual proportion of arthritis in whites infected in the East and the infrequence of salpingitis in the natives of Greenland. The complement fixation reaction is regarded as valuable in diagnosis, particularly the further the organism has ascended. The menstrual cycle is seen as the best provocative for reactivation of cervical lesions. Sooner or later, it is stated, in one-third of the cases the disease ascends from its original focus.

The section on therapy is replete with suggested methods and drugs. The author apparently places most reliance in the colloidal silver preparations, of which a great many, apparently proprietary, preparations are mentioned. General measures are described as well as therapy for local foci. The Sturmdorf operation is highly commended. Infantile gonorrhea seems to heal as slowly under the recommended measures as with many not mentioned. An apparatus is pictured for long continued vaginal and vulvar irrigation. For trichomonas, a frequent concomitant, glycerin and bichloride are recommended; for post gonorrheal

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[3]**Gonorrheo Der Weiblichen Genitalorgane. Ein Grundriss ihrer Pathologie, Klinik und Therapie.** Von Dr. Robert Joachimovits, Priv.-Dozent für Geburtshilfe und Gynäkologie an der Universität Wien. Mit 45 teils farbigen Abbildungen und 6 mehrfarbigen Tafeln, Wilhelm Maudrich, Wien, 1933.

leucorrhea lactic acid preparations. Ninety per cent of cases need no operation, 40 per cent heal without treatment.

Under operative procedure the author remarks that radicalism is frequently the best choice, and that narrowing of the bases of the broad ligaments after total operations is followed by long continued pain. He is a proponent of vaccine treatment, feeling it has at least a partial specific effect. Recognizing its limitations he states that vaccine therapy succeeds or fails, depending upon whether or not a gonococcus antibody is produced in the body. Various other measures are described, diathermy, baths, roentgen ray and physical therapy.

There are copious footnotes, with references to recent literature and an appendix dealing with certain technical items referred to in the text.

PHILIP F. WILLIAMS.

Cotte has published a valuable contribution[4] on the pelvic sympathetic in gynecology. Historically, interest in the subject was first aroused by Jonnesco in 1898, but his claims never received much attention. Recently the sympathetic nerves have been resected for a number of conditions. Cotte employs the operation for severe dysmenorrhea, vaginismus, the pain of inoperable carcinoma of the cervix, essential neuralgia, cystalgia and pruritus. The author became convinced of the value of this presacral nerve resection since 1924, finding it easier and more efficacious than other attempts to transect the pelvic sympathetic. He details the anatomy of all of the pelvic sympathetic nerves. From the physiological standpoint, the French school believes in local sympathetic centers, that the nerves have both an afferent and efferent function, which is in sharp contrast with the English view which assumes that these nerves have a purely efferent function between the cord and periphery. He also gives the neurology of the lower cord and sympathetic.

The operative technics are described in detail. Leriche's adventitia resection of the hypogastric artery, which is removed for 2 or 3 cm. is outlined fully. For the presacral resection, Cotte uses a low Pfannenstiel incision, retracts the rectosigmoid toward the left, incises the peritoneum over the promontory, and resects the entire cellular layer lying between, on the left, the inferior mesenteric vessels and, on the right, the right common iliac, without injuring the middle sacral artery.

Cotte has used the operation quite extensively, 5 cases of inoperable carcinoma of the cervix, 125 cases of severe dysmenorrhea, 16 cases of pelvic neuralgia, 7 cases of vaginismus, 16 cases of dyspareunia, combined with other symptoms.

From his results, he judges that some uterine congestions, many leucorrheas and genital excitations, as well as pruritus may be cured. This monograph gives a purely personal viewpoint and experience. It certainly is well worth studying, but should be accepted with a great deal of reserve.

R. T. FRANK.

Fraenkel and Fels have prepared a very attractive photographic atlas[5] of microscopic diagnosis covering the field of obstetrics and gynecology, bound in such a fashion that one can see the text and the atlas figures simultaneously. There are 132 microphotographs, mainly low power, which illustrate the type of lesions which the German student must be prepared to diagnosticate at his state examinations and which likewise cover the material seen by the average

[4] **Chirurgie du Sympathique Pelvien en Gynécologie.** By Gaston Cotte. Masson et Cie, Paris, 1932.

[5] **Photographischer Atlas der geburtshilflich-gynäkologischen mikroskopischen Diagnostik.** L. Fraenkel und E. Fels. S. Karger, Berlin, 1933.

pathologist, dealing with gynecologic material. While the interpretation of these lesions requires a considerable degree of previous training, this small atlas should prove of real use to the student, the gynecologist, and the laboratory pathologist.

The book is recommended because it covers the essential lesions, is small, and has a compact text. Personally, I still feel that drawings, in which the author can exaggerate the essential features and bring out his own personal viewpoint, are preferable from a teaching point of view.

R. T. FRANK.

The second edition of Douay's *Gynécologie*[6] is of pocket manual size and is written with a verve and style usually missing in this class of compends. For example, he begins by saying that the three major symptoms that dominate gynecology are bleeding (pertes rouges), discharge (pertes blanches) and pain. In addition, genital prolapse and problems of sterility are additionally important. Throughout the little manual a similarly striking presentation will be found. The text contains nothing of interest to the specialist but should be of value for short review to the student, or as an aid to the general practitioner.

R. T. FRANK.

Regad has published a most elaborate, thorough and complete monograph[7] on the special and limited subject of torsion of the fallopian tubes. The monograph is beautifully gotten up, gorgeously illustrated, and contains the full literature.

The author has collected 201 observations of this fairly rare disturbance, of which 20 per cent occurred before puberty had been reached. Although quite normal tubes have been observed to undergo torsion, the most common lesion producing this trouble is the presence of an ovarian cyst.

Although of such limited scope, this monograph will prove of value for reference.

R. T. FRANK.

Item

American Board of Obstetrics and Gynecology

The next written examination and review of case histories for certification by the American Board of Obstetrics and Gynecology will be held, according to location of applicants, in various cities of the United States and Canada, on Saturday, December 9, 1933, at 2 P.M. For application blanks and further details, address, Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh, Pennsylvania.

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[6] **Gynécologie.** par E. Douay, ed. 2, G. Doin & Cie, Paris, 1933.

[7] **La Torsion des Trompes Utérines.** By Jean Regad. Libraire Camugli, Lyon.